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A STUDY OF THE CLINICAL AND METABOLIC EFFECTS OF 9α-FLUORO-11β-HYDROXY-17α-METHYLTESTOSTERONE (FLUOXYMESTERONE)

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9α-Fluoro-11β-hydroxy-17α-methyltestosterone, a halogenated testosterone known as fluoxymesterone†, has been found to have high anabolic potency and low toxicity (Stafford[6]). When administered orally to the rat, it is ten times as potent as methyltestosterone in stimulating the seminal vesicle and twenty times as potent in stimulating the levator ani, while its toxicity is less than that of methyltestosterone (Lyster, Lund and Stafford[5]). Clinical studies have shown that the effects of fluoxymesterone given orally are three times to eight times those of methyltestosterone relative to androgenicity in the hypogonadal male, and anabolism as measured by retention of nitrogen (Bartter[1], Council on Drugs[2], Gordan[3], and Kennedy[4]). Because of its low toxicity, oral effectiveness, and high potency, it has been felt that the anabolic influence of fluoxymesterone, and side effects, if any, should be ascertained in people requiring a potent anabolic hormone.

Material and Methods. 1. SUBJECTS. Three patients in a metabolic ward at Bird S. Coler Memorial Hospital and Home were selected for clinical observation and metabolic studies. Case 1, a 56-year-old man, had been treated for cirrhosis of the liver 7 years previously. Five years ago he had undergone a lumbar laminectomy for a varicosity of the dura mater, with subsequent lower extremity weakness progressing to paraplegia. Osteoporosis of the lumbar spine was present. This patient was anorexic, depressed, indifferent, withdrawn, with apparently lowered mentality. He complained of constant backache, and showed a disinclination towards any activity.

Case 2, a 66-year-old man, was hospitalized chiefly because of left hemiplegia, which followed a cerebral thrombosis. He was cooperative and mentally more responsive than Case 1, but reacted rather sluggishly and indifferently. Both his appetite and nutritional status were poor.

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†Supplies of this drug were made available to us through the courtesy of the Upjohn Company under the trade name, Halotestin.

A third patient, a 71-year-old man, became uncooperative and refused to participate further in the study after one week of control observations, so that data from only 2 cases are recorded.

2. PROCEDURE. A control period of 15 days preceded our use of the active preparation. During this time a placebo similar in appearance to fluoxymesterone was administered. During a second 15-day period, 5 mg. of drug were given daily. In the third period, also of 15 days' duration, the dosage of fluoxymesterone was increased to 10 mg. daily. A recovery period of 18 days followed, during which a placebo was substituted for the fluoxymesterone.

The weighed diets were supervised by a research dietitian, and daily nitrogen intakes were calculated. Twenty-four hour urinary specimens were collected throughout the study, with nitrogen and creatinine excretions determined on several 3-day pools of urine during each period. The urinary excretion of 17-ketosteroids was measured in two 3-day urinary pools toward the end of each of the first three periods, and in three 3-day pools toward the end of the recovery period. Total serum protein, albumin, total cholesterol, and cholesterol esters were determined once during each period for both subjects. Additional tests, including blood sugar, blood urea nitrogen, thymol turbidity, and cephalin flocculation, were performed several times during the study in each subject.

3. CLINICAL FINDINGS. No change in the status of Case 1, the 56-year-old man, was observed during the control period and during the first 12 days under fluoxymesterone treatment. On the 13th day, at a dosage level of 5 mg. daily, he began to show slight subjective improvement, and had a better appetite. By the 18th day of treatment, the 3rd day at a dosage level of 10 mg. daily, he was markedly better. A dramatic change seemed to have occurred in his mood. He became interested in his surroundings and was talkative and optimistic. His appetite was excellent, and his back pain had disappeared. Further improvement was noted through the 23rd day of treatment, the 8th day after beginning a daily dosage of 10 mg. For the remaining 7 days of drug administration and throughout the recovery period of 18 days, these changes persisted. Recurrence of back pain and diminution of appetite were noted one month after fluoxymesterone was discontinued. After 3 months without treatment, deterioration in his mental responses was apparent, and after 5 months, the subject had returned to his initial status.

There were no striking changes at any time in Case 2, the 66-year-old man. His appetite seemed to be slightly greater after 12 days of treatment with fluoxymesterone at a dosage level of 5 mg. daily, and there was slight improvement in mood and mental responses after 22 days of treatment, namely, on the 8th day at a dosage level of 10 mg. daily. No further differences were observed during the periods of treatment and recovery, nor during continued clinical observation for several months following the study.

No edema, cardiac failure, or other untoward reactions occurred in either subject at any time.

NITROGEN BALANCE. Case 1 was in slightly negative nitrogen balance during the control period, while Case 2 showed a positive balance (Table 1). When a 5 mg. dose of fluoxymesterone was given daily, there was an average increase in retention of nitrogen of 2.08 gm. per day for Case 1 and 1.30 gm. per day for Case 2. When the daily dose was raised to 10 mg., the average increase in retention of nitrogen over control values was 1.44 gm. per day for Case 1 and 0.58 gm. per day for Case 2. During the recovery period of 18 days, Case 1 showed a prompt decrease in nitrogen balance, as compared with the periods of drug administration, with an average difference from control values of plus 0.41 gm. per day. For Case 2, retention of nitrogen during the recovery period remained at a level similar to that present during administration of 10 mg. of fluoxymesterone daily, with an average difference from control levels of plus 0.59 gm. per day.

CREATINE EXCRETION. No consistent changes in creatine excretion were observed (Table 1). In Case 1, there seemed to be an increase in urinary creatine during the recovery period, while in Case 2, a rise above control levels occurred only while 5 mg. of fluoxymesterone were given.

URINARY 17-KETOSTEROIDS (TABLE 1). The average 24 hr. urinary 17-ketosteroid values for Case 1 were 14.3 mg.

TABLE 1.—NITROGEN BALANCE, CREATINE EXCRETION, AND URINARY 17-KETOSTEROIDS IN 2 MEN BEFORE, DURING, AND AFTER ADMINISTRATION OF FLUOXYMESTERONE

		Period			
Test	*Case*	*Control (15 days)*	*5 mg. daily (15 days)*	*10 mg. daily (15 days)*	*Recovery (18 days)*
Average Nitrogen Balance*	1	−0.22	+1.86	+1.22	+0.19
(gm./day)	2	+3.68	+4.98	+4.24	+4.23
Creatine Excretion†	1	0.11	0.11	0.09	0.16
(mg./day)	2	0.04	0.09	0.06	0.05
Urinary 17-ketosteroids‡	1	14.3	15.2	9.8	16.1
(mg./day)	2	6.8	6.7	5.8	6.9

*The number of determinations from which each average value is derived equals the number of days in the corresponding period divided by three.

†Average values given for each subject are obtained from urine collected in 3-day pools on the 1st through the 12th days of the control period, on the 7th through the 15th days of treatment with 5 mg. fluoxymesterone daily, on the 1st through the 9th days at a 10 mg. daily dosage level, and on the 4th through the 18th days of the recovery period.

‡Average values given are obtained from determinations done on 2 pooled 3-day specimens collected on the 7th through the 12th days of the control period, 2 such specimens collected on the 7th through the 12th days of the period during which 5 mg. were given daily, 2 such specimens collected on the 10th through the 15th days of a 10 mg. daily dosage, and 3 such specimens collected on the 10th through the 18th days of the recovery period.

TABLE 2.—BLOOD CHEMISTRIES IN 2 MEN BEFORE, DURING AND AFTER ADMINISTRATION OF FLUOXYMESTERONE

		Period			
Test	*Case No.*	*Control*	*5 mg. daily**	*10 mg. daily†*	*Recovery‡*
Total serum protein	1	6.9	6.8	7.3	7.5
(gm./100 ml.)	2	7.1	6.2	8.2	7.1
Serum albumin	1	4.9	4.6	5.1	5.0
(gm./100 ml.)	2	4.9	4.4	5.5	4.9
Total serum cholesterol	1	235	245	263	237
(mg./100 ml.)	2	211	250	307	235
Cholesterol esters	1	159	145	169	143
(mg./100 ml.)	2	182	114	183	150
Thymol turbidity	1	5.5	5.3	2.0	2.8
(units)	2	2.0	—	1.0	—
Cephalin flocculation	1	3+	—	2+	0
(at 48 hrs.)	2	0	—	0	—
Blood urea nitrogen	1	10.2	8.3	8.7	10.3
(mg./100 ml.)	2	14.3	10.0	9.8	—
Fasting blood sugar	1	98	94	—	100
(mg./100 ml.)	2	99	82	—	—

*After 13 days at a dosage level of 5 mg. daily.

†After 14 days at a dosage level of 10 mg. daily.

‡18 days after fluoxymesterone was discontinued.

during the control period, 15.2 mg. and 9.8 mg. when 5 and 10 mg. respectively, of drug were given, and 16.1 mg. during the recovery period. The average control value for Case 2 was 6.8 mg., with average values of 6.7 and 6.8 mg. during treatment with 5 and 10 mg. of drug daily, respectively, and with an average level during recovery of 6.9 mg. The decrease which occurred when 10 mg. of fluoxymesterone were given daily probably indicated some degree of suppression of endogenous androgen formation.

BLOOD CHEMISTRIES (TABLE 2). Total serum protein and serum albumin decreased slightly during the administration of 5 mg. of fluoxymesterone daily. After 29 days of treatment, during the last 14 days of which 10 mg. of fluoxymesterone were given daily, there seemed to be an increase in serum albumin and total serum protein which persisted after 18 days without treatment in Case 1 but had returned to control levels in Case 2 at this time.

In both subjects total serum cholesterol rose moderately after 29 days of treatment, but returned to control levels after fluoxymesterone was discontinued.

In Case 1, who had a history of cirrhosis of the liver, thymol turbidity and cephalin flocculation were abnormal during the control period, but returned toward normal after 29 days of treatment, with normal values obtained during the recovery period. These tests revealed normal values initially for Case 2, with no change observed toward the end of the therapeutic trials.

Levels for blood urea nitrogen fell slightly in both subjects during treatment at both levels of dosage.

Fasting blood sugar was not altered in either subject by the daily use of 5 mg. of fluoxymesterone for 13 days.

Clinical Observations. In addition to the 2 subjects mentioned above the effects of fluoxymesterone have been recorded in 7 patients. These patients represent several different types of condition and, in most instances, have received not only fluoxymesterone but also at some previous time one or more different androgenic preparations. Numbering of these cases will conform to the series in general.

Case Reports. CASE 4: A.R. This patient was a 37-year-old, well nourished and developed male with a diagnosis of schizophrenia, whose major complaints included weakness; poor memory; inability to concentrate; and lack of self-assurance. Neither his history nor his physical examination revealed any findings suggesting a physical basis for his complaints nor were any abnormal laboratory findings discovered in a routine type of examination. The average of several 24-hour urinary 17-ketosteroid excretions was 10.0 mg. Despite the absence of any positive physical data, it was felt that the characteristic nature of his complaints might justify a trial of an anabolic steroid. Fluoxymesterone was given by mouth, 10 mg. daily, and the patient reported for 7 visits at weekly intervals. During the first week he thought he obtained some relief. However, it was quite clear as treatment continued that he gained nothing whatsoever from the therapy and it was finally discontinued at the end of the 7th week.

CASE 5: A.J. This was a 45-year-old man who may be said to have "lived hard." He was a salesman by profession, had quite irregular hours, drank heavily and remained, for a major portion of his time, under considerable tension. He was first seen because of severe low back pain which had variously been attributed to osteoporosis, arthritis and slipped disc. At the time he was first seen by us, there was evidence of a fracture of approximately 4 vertebrae and the roentgenograms showed obvious advanced osteoporosis. This patient had a prolonged course of therapy with various agents and various adjuvant measures. He was at first given testosterone propionate 50 to 100 mg. daily in sesame oil intramuscularly and after a 3-weeks' stay in the hospital twenty 75 mg. pellets of testosterone propionate were inserted subcutaneously. There was some apparent improvement in this man's condition during the first 4 to 5 months of treatment but no objective change in the vertebral roentgenologic findings. At the end of 7 months, by which time

the pellets had obviously absorbed, he was placed on fluoxymesterone 10 mg. daily, and remained on this therapy for approximately 4 months. There was considerable relief from his symptoms, particularly the low back pain. However, there was still very little evidence of bony recalcification although one radiologist believed that the epiphyses of the vertebrae showed more condensation than before. We believe that this patient was benefited by fluoxymesterone but it is difficult to compare this with previously used androgens, as he was confined to his bed for a portion of the earlier therapy.

CASE 6: J.M. This 43-year-old male, a physician, had suffered from hypogonadism ever since early adolescence. His was an eunuchoid habitus, his testes were soft and small and his skin fine and silky. This individual first complained of weakness, lack of self-assurance, inability to make serious decisions, difficulty in facing people and in meeting them socially and considerable disinclination to exert himself in any way. Prior to the use of fluoxymesterone this patient had been given various forms of androgenic therapy, all with good results. It seems sufficient here to comment upon the comparative usefulness of the different agents. For a short time he took testosterone propionate 25 mg. in sesame oil intramuscularly three times weekly with a disappearance of practically all of his symptoms. In view of the fact that such injections were rather inconvenient, the patient was tried on buccal testosterone propionate 10 mg. twice daily. While he obtained some relief from this, the relief was not complete. Therefore, 8 pellets, each weighing 75 mg. were subcutaneously implanted. He absorbed these at about the rate of 0.5 mg. per pellet per day and from them obtained complete relief. Later, fluoxymesterone was successfully employed in daily doses of 10 mg., which he has now used for more than one year.

CASE 7: A.S. This 36-year-old man has been under observation for approximately 10 years because of eunuchoidism, probably associated with a craniopharyngioma, which exhibited its first symptoms in late adolescence. This patient tried buccal testosterone propionate as well as methyl testosterone orally. Neither of these seemed to be very helpful. Testosterone propionate, 25 mg. intramuscularly three times weekly afforded him very good replacement although by no means complete relief. Maximum relief was obtained by the implantation of six 75 mg. pellets subcutaneously. These were absorbed at an approximate rate of 3.0 mg. daily, thus lasting from 4 to 6 months per implant. The need for reimplantation was readily appreciated by him because at such times, he would develop a recurrence of (1) loss of self-assurance; (2) lack of concentrating ability; (3) excessive shyness and unwillingness to make social or business contacts; (4) muscular weakness; (5) pastiness of face, and so forth. Fluoxymesterone proved to be excellent replacement therapy and the patient uses from 5 to 10 mg. daily as he may feel the need. This is the only medication that has proved as satisfactory for him as the implantation of pellets.

CASE 8: A.C. This was a 55-year-old man with outspoken climacteric symptoms. His chief complaints were "easy perspiration," tiredness out of all proportion to the work done, difficulty in concentrating, and excessive irritability. The physical examination was essentially negative. His 17-ketosteroid excretion was 8 mg. per 24 hours. He was placed upon 25 mg. of testosterone propionate in oil injected intramuscularly three times weekly. He was free of complaints at the end of the second week and was immediately switched to 5 mg. of fluoxymesterone daily. This maintained control of his symptoms. After 5 weeks the medication was stopped. There was a recurrence of symptoms 4 weeks later and these were again relieved by the same medication. This was again stopped after 4 weeks. About 3 months later there was further recurrence of the same manifestations. At this time a placebo identical in appearance to fluoxymesterone was used without any influence whatsoever upon the symptoms. Without the patient's knowledge, fluoxymesterone was then substituted for the placebo with complete relief of symptoms. We consider this an excellent result. Attempt is now being made to taper the medication so that the patient receives a dose of fluoxymesterone once in 3 days. So far there has been no recurrence of symptoms while taking this reduced dose.

CASE 9: H.K. This was a 60-year-old man who first came to us 3 years ago complaining of loss of weight, loss of muscular strength, easy fatigability and inability to concentrate. This man has been a somewhat heavy drinker; he is in the advertising business where there is continuous sales contact and selling pressure. He was persuaded to give up alcohol entirely and to reorder his life in such fashion that some of the selling pressure was removed. Inasmuch as he was virtually operating his own business, this was possible and he carefully cooperated. However, despite a much reduced activity and despite full correction of his dietary, working and sleeping

hours, this patient still did not gain back lost weight and complained of muscular weakness, lack of concentrating ability and easy fatigability. For these reasons various testosterone preparations were tried. He was first given buccal testosterone, 10 mg. three times daily, with considerable relief of symptoms. Later, eight 75 mg. pellets were subcutaneously implanted. This gave him reasonable relief of symptoms but the action was not well sustained and disappeared entirely in about 4 months. Finally, he used fluoxymesterone 5 mg. daily which afforded him complete relief of symptoms. He now uses the material intermittently. As soon as all of the symptoms are well controlled, he stops the medication. At the beginning of the return of symptoms, the medication is again started. He has slowly gained weight and muscular strength. He still finds he tires more easily than he should and he also finds that his sleep is not as good as it should be. Tranquilizing agents have relieved the sleeping problem. It is believed that the intermittent use of fluoxymesterone will eventually control the other symptoms completely.

CASE 10: M.D. This 51-year-old man had had well proven climacteric symptoms for about 6 years. He had only intermittently needed injections of testosterone propionate in oil. At the time of our first examination, his 17-ketosteroid excretion was low (10.3 mg. per 24 hours). Prominent among the symptoms present in this individual were arthralgias, particularly involving the knees, elbows and all joints of the hands and feet. In fact, the patient's condition had, prior to seeing us, been diagnosed as a chronic osteoarthritis of the "degenerative" type. This patient is completely free of his symptoms, using 5 mg. of fluoxymesterone daily. It is usually necessary for him to continue this dosage for from 2 to 3 weeks. Medication is then completely stopped. At the first return of symptoms, the medication is again started. In this way, the patient has used fluoxymesterone for almost 2½ years with good results, and actually takes the medication perhaps one-third to one-fourth of the time.

Discussion. Fluoxymesterone appears to be a potent androgen some three to six times as active as methyltestosterone. In hypogonadal men Gordan found the compound approximately five to fifteen times as potent androgenically as its nonhalogenated analogue[3]. Kennedy has considered the drug "at least five times as potent as methyltestosterone in humans"[4]. We have had no opportunity to compare the compound with methyltestosterone as far as the retention of nitrogen is concerned. However, that it will retain nitrogen is quite clear from our balance studies as well as those of others (Bartter[1], Council on Drugs[2], Gordan[3] and Kennedy[4]). Kennedy[4] believes the compound has an anabolic/androgenic ratio which is greater than one. In small laboratory animals the androgenic activity measured by the weight of the seminal vesicle is nine and a half times that of methyltestosterone, whereas the anabolic activity measured by the levator ani weight technique is twenty times that of methyltestosterone (Bartter[1]). While creatinuria has been described (Kennedy[4]) it did not occur in 2 of our patients for whom the urinary excretion of this metabolite was measured.

We have been unable to find in the literature any notation of the influence of fluoxymesterone upon the urinary levels for 17-ketosteroids. In the present studies such levels were apparently unaffected by 5 mg. daily and depressed by 10 mg. daily. It would seem then that for the periods of time observed 5 mg. will not influence the endogenous production of 17-ketosteroids precursors, whereas, 10 mg. daily will. These observations also are indicative of the fact that the metabolism of fluoxymesterone probably follows the same pathways as those now well-known for testosterone.

Little attention was paid to the reported values for total serum cholesterol, while these studies were in progress. When tabulated, it becomes rather clear that consistent increases in cholesterol occurred under treatment with the compound in both patients who participated in the metabolic studies and returned to approximately

pre-treatment levels during the recovery period.

There seems to be little doubt that fluoxymesterone is a potent androgen with high anabolic activity. However, more observations on human beings are necessary before its full advantages and disadvantages can be sharply defined.

Summary. Two men were subjected to metabolic and clinical studies before, during, and after the administration of fluoxymesterone (Halotestin) at dosage levels of 5 and 10 mg. daily.

Marked clinical improvement occurred in one patient, who had shown both mental and physical deterioration prior to treatment; this was maintained for at least one month after treatment was discontinued. A second patient, in relatively good condition prior to treatment was not strikingly changed by administration of the steroid, although nitrogen balance became more positive.

Fluoxymesterone, at a dosage level of 5 mg. daily, caused a definite increase in the retention of nitrogen. No further increased occurred when the dosage was doubled. Within 3 days after fluoxymesterone was discontinued, balances for nitrogen had decreased.

Urinary 17-ketosteroid levels were decreased during administration of 10 mg. daily of fluoxymesterone.

Serum protein, albumin, and total cholesterol were slightly increased when 10 mg. of fluoxymesterone were given daily. A decrease in previously abnormal values for thymol turbidity and cephalin flocculation occurred in one formerly cirrhotic subject. Blood urea nitrogen was slightly lowered during treatment, while blood sugar was unchanged.

In addition to the 2 men upon whom nitrogen balance studies were performed, 7 other patients have been given fluoxymesterone for varying periods of times, ranging from approximately 6 weeks to more than 2½ years. These patients have suffered respectively from schizophrenia; osteoporosis; eunuchoidism (2 patients) and the male climacterium (3 patients). No appreciable improvement was obtained in the patient with schizophrenia. Improvement of varying degree has been noted in the other 6 patients.

It is our conclusion that fluoxymesterone is an effective androgen with good metabolic action. It is not possible from the present studies to compare its androgenicity and anabolic actions successfully. However, we are inclined to believe that it is androgenic in direct proportion to the degree in which it is anabolic. It represents an effective method of introducing an anabolic androgen orally.

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SUMMARIO IN INTERLINGUA

Un Studio Del Effectos Clinic e Metabolic De 9α-Fluoro-11β-Hydroxy-17α-Methyltestosterona (Fluoxymesterona)

Duo homines esseva subjicite a studios metabolic e clinic ante, durante, e post le administration de fluoxymesterona (Halotestina) a nivellos de dosage de 5 e 10 mg per die.

Marcate grados de melioration clinic occurreva in un del patientes le qual habeva monstrate signos de deterioration mental e physic ante le tractamento. Isto esseva mantenite durante al minus un mense post que le tractamento habeva essite discontinuate. Le secunde patiente, in relativemente bon condition ante le tractamento, non esseva alterate frappantemente per le administration del steroide, sed al minus le balancia de nitrogeno deveniva plus positive.

Fluoxymesterona, in doses de 5 mg per die, causava un definite augmento del retention de nitrogeno. Duplar le dosage non resultava in un augmento additional. Intra 3 dies post le cessation del administration de fluoxymesterona, le balancias de nitrogeno se monstrava reducite.

Le nivellos urinari de 17-cetosteroides esseva reducite durante le administration de 10 mg de fluoxymesterona per die.

Proteina, albumina, e cholesterol total del sero esseva levemente augmentate quando 10 mg de fluoxymesterona esseva administrate diurnemente. Un reduction de previemente anormal valores in le turbiditate a thymol e in le flocculation a cephalina occurreva in un subjecto qui habeva essite cirrhotic. Le nitrogeno de urea in le sanguine esseva levemente reducite durante le tractamento, sed le sucro del sanguine monstrava nulle alteration.

A parte le 2 homines in qui studios del balancia de nitrogeno esseva effectuate, 7 altere patientes recipeva fluoxymesterona durante varie periodos de tempore, ab circa 6 septimanas usque a plus que 2½ annos. Le suffrentia de iste patientes esseva schizophrenia (1 caso), osteoporosis (1 caso), eunuchoidismo (2 casos), e climacterio mascule (3 casos). Nulle appreciabile melioration esseva obtenite in le patiente con schizophrenia. Varie grados de melioration esseva notate in le altere 6 patientes.

Nostre conclusion es que fluoxymesterona es un efficace androgeno con bon action metabolic. Super le base del presente studios, il non es possibile comparar su androgenicitate e su effectos anabolic de maniera satisfactori. Tamen, nos tende a creder que le agente es androgenic in proportion directe al grado a que illo es anabolic. Illo representa un methodo efficace pro le introduction oral de un androgeno anabolic.

THE EFFICACY OF CORN OIL IN LOWERING THE SERUM CHOLESTEROL OF PATIENTS WITH CORONARY ATHEROSCLEROSIS*

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Several authors have recently pointed out that the ingestion of highly unsaturated fats under controlled conditions was usually associated with a lowering of serum cholesterol, particularly if the previous diet had contained abundant amounts of fat from animal sources (Ahrens *et al.*[1], Beveridge, Connell and Mayer[3], and Bronte-Stewart *et al.*[4]). In these studies, corn oil was unsurpassed by any other fat in its cholesterol lowering potency. We were interested as to whether this effect could be achieved in actual clinical practice, where diets are not rigidly controlled. Moreover, most Americans are used to eating meat twice a day, and it was uncertain whether corn oil in combination with saturated fats from this much meat would have its usual effect in lowering serum cholesterol.

Methods. Twenty-three patients with clinical coronary atherosclerosis were selected for this study. Fifteen of them had a previous history of myocardial infarction, and 18 of them were suffering from angina pectoris. After determining control levels of serum cholesterol, the patients were instructed to ingest 1 to 1½ ounces of corn oil (Mazola) before each meal. Various methods were employed to increase its palatability. Usually the corn oil was emulsified in some aqueous flavoring agents. Since the corn oil was taken before meals, very few patients had any significant weight gain. The use of corn oil as a salad oil and a cooking oil was also encouraged. Five of the patients were told to drink the corn oil and were given no additional dietary restrictions whatsoever. In 18 other patients, our aim was to change the ratio of linoleic to saturated fatty acids in the diet as much as possible while still allowing meat twice a day. In these patients the usual dosage of corn oil was prescribed, but instructions were also given to avoid butter fat, margarine, various hydrogenated vegetable oil preparations, and more than one egg a day. Six of these 18 patients had been on a low fat diet before starting on the corn oil regimen. Most of them felt that the more liberal corn oil regimen was considerably easier and more pleasant to follow than the strict low fat diet. Cholesterol was determined by the Schönheimer-Sperry method. In certain patients the phospholipid phosphorus of serum was also determined by the method of Youngburg. This value was multiplied by the conventional factor of 25 to get an estimate of the total phospholipid concentration.

Results. The results for the individual patients are shown in Table 1. Sixteen of the 23 patients (70%) had at least a 15% drop in serum cholesterol on the corn oil regimen. As shown in Table 1, 5 of these 16 had been on a fat-restricted diet during the control period but nevertheless showed at least a 15% decrease in cholesterol. The average pre-treatment cholesterol level for these 16 patients was 271 mg. per 100 ml. of serum. During the corn oil

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TABLE 1.—CHOLESTEROL AND PHOSPHOLIPID LEVELS IN THE SERUM OF CORONARY PATIENTS BEFORE AND DURING THE INGESTION OF CORN OIL

Pt.	Individual Pretreatment Cholesterol Levels (mg. %)§	Average Pretreatment Cholesterol Level (mg. %)	Individual Cholesterol Determinations During Corn Oil Regimen (mg. %)‡	Average Cholesterol Level During Corn Oil Regimen (mg. %)	% Decrease of Average Cholesterol Level During Corn Oil Regimen	Average Pretreatment Phospholipid Level (mg. %)	Average Phospholipid Level During Corn Oil Regimen (mg. %)
L.K.	275,248,284	270	159	159	−41%	285	200
H.M.	247,259,253	253	174,181,168,179 166 163,177	173	−32%		
J.C.*	305,297,313	305	202,184,225,210	206	−32%	293	240
P.O.	311,316,319	315	264,243,213,210	232	−26%		
L.W.*	189,192,193	191	136,147	141	−26%		
A.P.*	261,267,268	266	202,225,186,183	199	−25%	313	242
F.W.†	275,290,299	288	231,201	216	−25%	320	240
J.G.†	298,299,306	301	221,231,239	230	−24%	273	195
L.B.	162,163,175	167	128	128	−23%		
D.L.†	232,242,262,283	255	198,204	200	−22%	270	235
N.A.	270,298,308	292	270,253,260,216,227 212,227,230,215	235	−20%		
T.D.	259,284,361	301	240,248	244	−19%	285	255
G.S.†	299,304,313,325	311	260,254,271	262	−16%	283	257
V.S.	308,313,328 331,347	325	269,275,285,268	274	−16%		
M.H.	262,264	263	218,225	222	−16%	260	220
J.D.†	239,239,242 214,255	238	201,202	202	−15%		
D.A.	313,316,288 324,331	314	261,281	270	−14%	288	277
M.B.	266,290,306	288	227,259,252	246	−14%	263	247
S.G.†	253,255,256,278	261	227	227	−13%	260 275	222 255
G.W.†	284,297	291	246,253,255	252	−13%		
F.L.*	306,320,324	316	278,282,288	283	−11%		
A.A.*	152,175,186	171	148,163	155	−9%		
L.W.†	235,246,251 259,283	254	260,235	247	−3%		

* Patients who were given no dietary instructions or restrictions other than directions for taking corn oil.
† Patients who were on a low fat diet during the control period before starting corn oil.
‡ Only cholesterol levels obtained after 12 days on the corn oil regimen are listed.
§ mg. % indicates mg. per 100 ml. of serum.

regimen the cholesterol level fell to an average value of 208, a 63 mg. drop. Serum phospholipids were determined in half of this group. The average pretreatment phospholipid level was 287 mg. per 100 ml. of serum. The average phospholipid level fell to 231 during the corn oil ingestion.

Six other patients, 26% of the total group, had smaller decreases of 9% to 14% in serum cholesterol while taking corn oil. The average pretreatment level for this group was 274, while the average level during the corn oil program was 239, a drop of 35 mg. per 100 ml. of serum. The phospholipids were determined in two-thirds of this group and dropped from an average of 272 mg. per 100 ml. of serum before treatment, to 250 during the corn oil feeding.

One patient had no significant change in serum cholesterol at all. Very frequently a sizable decrease in serum cholesterol was apparent after only a week of corn oil ingestion. In a few patients the response was more delayed and the cholesterol would continue to decrease slowly for a month after starting corn oil. One patient (N.A.) had an initial minor decrease in cholesterol 2 weeks after starting corn oil. His cholesterol concentration was stabilized at this level for 3 months and then underwent a further sizable decrease which has been maintained for 2 months. One patient (H.M.) obtained a maximum cholesterol response 2 weeks after beginning corn oil. This lower level has been maintained for the succeeding 12 months. After 2 patients had obtained their maximum effect from corn oil, they were given 4 gm. of β-sitosterol (Cytellin, Lilly) with each meal for 6 weeks while they continued to take corn oil. The β-sitosterol in combination with corn oil did not produce a lower cholesterol level than was attained with corn oil alone.

A fourth of the patients had slight indigestion while taking 1½ ounces of corn oil with each meal. Only one in 23 had indigestion while taking 1 ounce with each meal, and he had an active duodenal ulcer. The cholesterol lowering effect could usually be obtained with 1 ounce of corn oil before each meal. Doses smaller than this were not explored. Five patients reported considerable relief from anginal attacks while ingesting corn oil. However, this seeming improvement is very difficult to evaluate since it is well known that placebo therapy can greatly relieve anginal symptoms. No patient reported an increase in anginal pain while participating in the corn oil program.

A decrease in serum cholesterol following corn oil ingestion was usually accompanied by a lowering of serum phospholipid (Table 1). This would inevitably be the result of a decrease in the concentration of one or several species of serum lipoproteins, since both cholesterol and phospholipid make up an integral part of both α and β lipoproteins.

These results are highly significant, statistically. If corn oil were having no real effect on the serum cholesterol and phospholipid levels, then one would expect from random variation as many increases in concentration during corn oil ingestion as there were decreases. Actually all the patients, without exception, had decreases in the concentration of cholesterol and phospholipid while eating corn oil.

Comment. Men with a history of myocardial infarction, on the average, have definitely higher serum cholesterol levels than age-matched men without a history of infarction (Gertler, Garn and White[6]). Also, populations with low average cholesterol levels, such as the Chinese, Japanese, or Bantu, have a lower incidence of coronary disease than populations with much higher average levels, such as are ob-

served in the United States (Dock[5], Keys[7], and Snapper[8]). Thus, the circumstantial evidence suggests that the lower the serum cholesterol, the lower the incidence of myocardial infarction. For this reason, we felt justified in treating coronary patients with so-called "normal" cholesterol levels.

In 70% of our coronary patients the corn oil regimen produced a considerable decrease in serum cholesterol. This does not, however, necessarily certify it as an effective therapeutic measure. A drop in serum lipoprotein produced in this way, may or may not be clinically beneficial. This must be decided by further studies. The mechanism by which the corn oil lowers serum cholesterol is still very obscure. Linoleic acid constitutes 56% of the fatty acids in corn oil. Oleic acid accounts for another 30%, and various saturated fatty acids, particularly palmitic acid and stearic acid, account for 14%. Whether the linoleic acid, or substances other than triglycerides, or both, cause the lowering of serum cholesterol is a question we hope will be resolved by further studies. We have some preliminary evidence that linoleic acid is not wholly responsible for the decrease in serum cholesterol. In our patients safflower oil, which contains 29% more linoleic acid than corn oil, was not quite as effective as corn oil in lowering serum cholesterol. A similar result was obtained when various fats were fed to 128 freshman medical students at the University of Minnesota School of Medicine. In this study 2 oz. of corn oil were given to one group each day and 2 oz. of safflower oil were given to another group. At the end of 9 days the change in cholesterol was ascertained. Those students on corn oil had an average decrease of 11.2% in their serum cholesterol. The group taking safflower oil had only an 8.9% decrease in cholesterol (Armstrong *et al.*[2]). If linoleic acid were the only factor concerned, the safflower oil should have been more potent in lowering serum cholesterol. Since it was slightly less potent, we must conclude that corn oil has some other property active in depressing cholesterol levels.

Since our patients taking corn oil did not usually gain weight, their intake of other foodstuffs must have been curtailed. Moreover, their intake of saturated fats was also curtailed. This undoubtedly contributed to the decrease in serum cholesterol (Beveridge, Connell and Mayer[3]).

Case Report. A 42-year-old man had anginal symptoms for 2 years, with a normal electrocardiogram but definitely positive electrocardiographic findings during an exercise test. His three control levels of serum cholesterol during May, June, and July of 1956, were 247 mg. per 100 ml. of serum, 259, and 253, respectively. On July 13, he started taking 1¼ ounces of corn oil before each meal. On July 20, his cholesterol concentration was 192. On August 17, it was 174. On September 14, it was 181. On October 17, it was 168. The cholesterol was determined four more times during 1956 and never rose above the 177 level of December 24, 1956. These low levels were continuously maintained throughout the first half of 1957. Symptoms of chest pain brought on by exertion were considerably less frequent during the last 5 months of 1956 and the first 6 months of 1957 than in the first 6 months of 1956.

Summary. Twenty-three patients with coronary disease ingested 1 to 1½ ounces of corn oil three times a day, either undiluted or emulsified with flavored water. In addition they used corn oil as a cooking and salad oil. Five of the patients were given no other diet restrictions; 18 we instructed to eat very little butter fat or hydrogenated vegetable fats. Lean meat and all other items in the diet were allowed *ad libitum*. Seventy per cent of the patients had at least a 15% decrease in serum cholesterol. Their pre-treatment cholesterol level averaged 271 mg. per

100 ml., while their average level was 208 after a period on corn oil. Another 26% of the patients had smaller decreases of 9% to 14% in serum cholesterol while taking corn oil. Serum phospholipids were also depressed during corn oil ingestion. The drop in cholesterol has been continuously maintained during a whole year of corn oil ingestion. None of these patients had any exacerbation of angina pectoris while taking corn oil.

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SUMMARIO IN INTERLINGUA

Le Efficacia De Oleo De Mais In Reducer Le Cholesterol Del Sero De Patientes Con Atherosclerosis Coronari

Vinti-tres patientes con morbo coronari ingereva inter 1 e 1½ uncias de oleo de mais tres vices per die, o non-diluite o emulsificate con aqua aromatic. In ultra, illes usava oleo de mais in cocer e como oleo de salata. Cinque del patientes habeva nulle altere restriction dietari a observar. Dece-octo recipeva le instruction de mangiar pauchissime grassia de butyro o hydrogenate grassias vegetal. Carne magre e omne altere componentes del dieta esseva permittite liberemente. In 70 pro cento del patientes, il occurreva un reduction del cholesterol seral de al minus 15 pro cento. Le valor medie de lor nivellos de cholesterol ante le tractamento esseva 271 mg per 100 ml, e le correspondente valor post un certe periodo del uso de oleo de mais esseva 208 mg per 100 ml. In 26 pro cento additional del patientes, il occurreva un minus marcate reduction del nivello de cholesterol in le sero durante le ingestion de oleo de mais. In iste gruppo le reduction amontava a inter 9 e 14 pro cento. Etiam le phospholipidos del sero esseva deprimite durante le ingestion de oleo de mais. Le reducite nivello de cholesterol ha essite mantenite continuemente durante un anno integre de ingestion de oleo de mais. Nulle del patientes experientiava un exacerbation de angina de pectore durante le regime a oleo de mais.

SERUM BETALIPOPROTEIN STUDIES IN THE SOUTH AFRICAN BANTU*

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Studies in geographical pathology indicate a wide variation in the incidence of coronary atherosclerosis in different populations. Clinical and pathological observations in Japan (Kimura[14]) and South Africa (Becker[2], Elliott[7] and Higginson and Pepler[11]) have demonstrated a remarkably low incidence of the disease in the native population of these countries.

From the clinical experience of one of us (H.R.), it was apparent that coronary artery disease in the South African Bantu is rarely seen, in striking contrast to its frequent occurrence in the white population of this same country. Becker[2], in 3,000 consecutive necropsies on Bantu and mixed subjects, found coronary thrombosis to be the cause of death in only 4 instances. Higginson and Pepler[11] reported 7 cases of coronary thrombosis or myocardial infarction and one case of ischemic heart disease in 1,328 Bantu necropsies. Grek, quoted by Elliott[7], analysed 6,000 Bantu patients admitted to one hospital in Johannesburg during a 6-year period. Twenty-two cases were thought to have myocardial infarction but some 15 of them were finally attributed to stenosis of the coronary ostia due to syphilis. Three of the remaining 7 cases were necropsied and 2 of these were found to have coronary thrombosis. By contrast, in 8,000 admissions of white patients to the Johannesburg General Hospital during a 2-year period, there were 235 cases of coronary thrombosis. In addition, Gelfand[8] in Southern Rhodesia, Williams[17] and Davies[5] in Uganda and Edington[6] working in West Africa have all noted a remarkably low incidence of coronary thrombosis and myocardial infarctions in Africans.

On the basis of the observed low incidence of coronary thrombosis it was felt that a study of the serum betalipoproteins of the Bantu would be of interest because of the association of these substances with atherosclerosis. A cooperative study was arranged whereby samples of blood were collected in Johannesburg, under the supervision of one of the authors (B. M.B.), preserved and flown to this country.

Methods and Materials. The subjects used in this study came from the following sources: A) Adult males recently arrived in Johannesburg from bush country areas. B) Adult males from the wards of the Coronation Hos-

*Some of the data reported in this study formed part of an exhibit on atherosclerosis shown at the American Medical Association Annual Meeting at Atlantic City in June, 1955.

pital, Johannesburg, a hospital devoted entirely to the care of the Bantu population. The majority of those chosen were patients in the surgical wards who were convalescing from injuries, care being taken to eliminate patients in whom obvious medical disease coexisted. C) Male and female subjects living in the environs of Johannesburg who are employed as domestics or in industries.

Each individual was submitted to a clinical survey including history, dietary habits and physical examination. They were classified roughly according to body habitus and at the same time that blood was taken for ultracentrifuge analysis, various laboratory studies were carried out, which consisted in the main of hemoglobin estimations, serological tests for syphilis, serum proteins, cholesterol and a complete lipid survey. Urinalysis, liver function tests and other investigative procedures were carried out where indications existed.

All blood samples for lipoprotein studies were drawn after a 12-hour fast, preserved with Merthiolate, refrigerated in containers and flown to this country, where they were processed within 24 hours of arrival, following which ultracentrifuge analysis was performed according to the technique of Gofman. The S_f 12–20 and S_f 20–100 lipoprotein classes were evaluated because of the association of these segments of the lipoprotein spectrum with coronary atherosclerosis. The ultracentrifuge films were read by one of us (I.J.G.) without any knowledge of the identity of the samples and the correlation of the data was made only after the reading of the films had been completed.

The purpose of this communication is to report the serum betalipoprotein levels found in Bantu subjects of South Africa. Details of the total lipid spectrum including cholesterol as it exists in these same individuals will form the basis of a subsequent report.

Results. A total of 339 samples were studied. There were 248 males and 91 females in the series. Tables 1 and 2 list the averages of the S_f 12–20 and 20–100 classes of serum betalipoprotein values in mg. per 100 ml. according to age and sex. Table 3 shows the values based on 959 "clinically normal" individuals of both sexes in a sampling of the white population of New York City, as determined in the same laboratory. These values serve as arbitrary figures for the purposes of comparison in this study. It will be observed that the Bantu levels are markedly lower in all age groups in both sexes. Two

TABLE 1.—SERUM BETALIPOPROTEIN VALUES IN BANTU MALES (248)

Age	*No. Cases*	*S_f 12–20 (mg./100 ml.) Average*	*S_f 20–100 (mg./100 ml.) Average*	*Abnormals*
Under 20	55	20	28	5
20 to 29	62	18	27	3
30 to 39	51	16	24	0
40 to 49	44	18	23	2
50 to 59	25	19	30	0
Over 60	11	21	28	0

TABLE 2.—SERUM BETALIPOPROTEIN VALUES IN BANTU FEMALES (91)

Age	*No. Cases*	*S_f 12–20 (mg./100 ml.) Average*	*S_f 20–100 (mg./100 ml.) Average*	*Abnormals*
Under 20	22	24	30	6
20 to 29	24	21	29	2
30 to 39	20	25	32	2
40 to 49	12	27	34	1
50 to 59	3	47	62	1
Over 60	10	32	43	2

interesting observations are worthy of mention. Firstly, the average serum betalipoprotein levels are higher in the Bantu females in each age group when compared with the corresponding Bantu male group. Secondly, while the levels rise somewhat with increasing age in the females, they remain at the same level throughout all the male groups. It will be noted that in several of the groups there are only a small number of subjects, as a result of which no statistical value can be attributed to the findings. However, there is evidence of a trend which we hope to explore in a subsequent expanded study.

TABLE 3.—SERUM BETALIPOPROTEIN VALUES IN "CLINICALLY NORMAL" NEW YORK CITY WHITE INDIVIDUALS

Age	No. Cases	S_f 12–20 (mg./100 ml.) Average	S_f 20–100 (mg./100 ml.) Average
A. Males (681)			
20 to 29	46	29	50
30 to 39	100	36	56
40 to 49	117	40	63
50 to 59	278	44	69
60 to 69	89	39	57
70 to 76	51	36	42
B. Females (278)			
13 to 19	34	19	34
20 to 29	61	24	53
30 to 39	46	31	50
40 to 49	29	35	58
50 to 59	47	41	60
60 to 69	42	40	54
70 to 79	19	30	49

Since all the female subjects were urban dwellers, it became necessary to subdivide the male individuals into urban and rural groups for comparison. However, no significant difference in serum betalipoprotein levels was found in the two groups of males on the basis of habitat as shown in Table 4.

Of 248 males, only 10 (4%) showed elevated S_f 12–100 levels when compared with "normal" New York City standards. On the other hand, 14 (15%) of 91 females were found to have elevated levels by the same standards.

Discussion. The results of this study demonstrate a marked difference between the levels of the S_f 12–100 classes of serum betalipoproteins in South African Bantu subjects and New York City white individuals. The low levels found in the Bantus who are almost exempt from coronary thrombosis would appear to confirm the observation of Gofman *et al.*[9] as to the relationship between the above group of serum betalipoproteins and this disease.

It is unlikely that the difference between the two groups is an ethnic one since there is no evidence that serum lipids are influenced by racial origin. Bersohn and Wayburne[3] have recently demonstrated a lack of difference in the cholesterol concentration of white South African and Bantu infants despite the fact that there are marked differences in the concentration of this substance in the adult population of the two racial groups. Several Bantu subjects with chronic glomerulonephritis, malignant hypertension or diabetes mellitus, and, therefore, not included in this study, exhibited raised serum betalipoprotein levels in a manner identical with that noted in white patients suffering from the same diseases (Table 5). These findings serve to demonstrate the fact that the Bantu is capable of developing raised serum betalipoprotein levels in the presence of atherosclerogenic disease.

An interesting observation is the paradoxical finding of higher serum betalipoprotein values in the female Bantu when compared with the male, and the rising levels in the female with increasing age. Although differences in physical activity and the more frequent

occurrence of obesity in the female may play a role in this variation, there are at present no data from which conclusions may be drawn.

It is generally agreed that the Bantu diet is low in fat, comprising approximately 20% of the calorie intake (Batson[1]). While the total calorie value is fairly adequate, the diet is also relatively deficient in animal and total protein, consisting largely of mealie meal. This is a flour made from corn which is cooked and eaten in considerable quantities, forming the basis for each meal. Although the urban Bantu is tending to change his eating habits so that they resemble those of the white South African a little more closely, the inclination is to prefer carbohydrates to protein with relatively little interest in fats, possibly because of the economic factor. With the recent work on the action of unsaturated fatty acids, especially corn oil on serum cholesterol, the possibility arises that the prolonged daily ingestion of large quantities of mealie meal may exert a protective effect against atherosclerosis.

TABLE 4.—COMPARISON OF SERUM BETALIPOPROTEIN VALUES IN BANTU BUSH AND URBAN DWELLERS (MALE)

	No. Cases		*Average S_f 12–20 (mg./100 ml.)*		*Average S_f 20–100 (mg./100 ml.)*	
Age	*Bush*	*Urban*	*Bush*	*Urban*	*Bush*	*Urban*
Under 20	32	23	21	18	31	24
20 to 29	48	14	19	22	28	27
30 to 39	30	21	15	16	24	24
40 to 49	18	26	15	20	26	25
50 to 59	5	20	19	20	26	31
Over 60	2	9	13	23	24	29
Totals	135	113				

TABLE 5.—ILLUSTRATIVE CASES OF ABNORMAL SERUM BETALIPOPROTEIN VALUES IN BANTU SUBJECTS ASSOCIATED WITH DISEASED STATES

1. Bantu male, aged 40, malignant hypertension	S_f 12–20 = 108 mg. S_f 20–100 = 128 mg.
2. Bantu male, aged 61, diabetes mellitus	S_f 12–20 = 73 mg. S_f 20–100 = 100 mg.
3. Bantu male, aged 6, nephrotic stage of glomerulonephritis	S_f 12–20 = 78 mg. S_f 20–100 = 60 mg.
4. Bantu male, aged 45, severe hypertension	S_f 12–20 = 62 mg. S_f 20–100 = 65 mg.
5. Bantu female, aged 34, diabetes mellitus	S_f 12–20 = 84 mg. S_f 20–100 = 140 mg.

Chronic liver disease is an ever present problem when one studies metabolic processes in the Bantu. While its effects cannot as yet be stated with certainty, we do have some information. Walker and Arvidsson[16] were unable to demonstrate any difference in the mean serum cholesterol levels in Bantu subjects with or without liver disease. Estimation of the percentage

of cholesterol esters in the subjects which form the basis of the present study shows them to be within normal limits. However, an abnormality of hepatic function may be involved insofar as the sex hormones are concerned in that changes in the androgen-estrogen balance may help to explain the low serum betalipoprotein pattern in these individuals. Since varying degrees of feminization are commonly observed in the Bantu male, the possibility is worthy of further study.

Although severe coronary atherosclerosis is far less common in the Bantu than in the white population of South Africa, it does occur with sufficient frequency to suggest that there is a discrepancy between its occurrence and the rarity of coronary thrombosis. The inadequately documented but widely held view that thromboembolic disease in general is uncommon in the Bantu (Keys[12]) may explain such a discrepancy; that is, not only is coronary atherosclerosis less severe but there is also a diminished tendency for coronary thrombosis to occur in the presence of atherosclerosis. Another aspect of deficient liver function which, therefore, also remains to be investigated is the possibility that there is present a subtle defect in the clotting mechanism which renders the Bantu less liable to intravascular thrombosis. A recent study in our laboratory (Black, Wayne and Greenblatt[4]) showed that the conversion of proconvertin to convertin in untreated patients with coronary thrombosis is twice as rapid as in a group of normal individuals. On the other hand, the decreased incidence of clotting may be related to a low fat intake as suggested by the recent work of Grieg[10] on the inhibition of fibrinolysin by alimentary lipemia, and that of other workers (Keys *et al.*[13], and O'Brien[15]) who have demonstrated acceleration of blood coagulation following the ingestion of fats.

Conclusion. 1. The adult male and female South African Bantu exhibits levels of serum betalipoproteins of the S_f 12–100 classes which are significantly lower than those of "clinically healthy" white New York City individuals.

2. These findings may be related to the Bantu dietary.

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(Interlingua on page 156)

CARDIAC FUNCTION DURING LIPEMIA: A STUDY IN FORCE BALLISTOCARDIOGRAPHY

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Deterioration of myocardial function following a fatty meal would not be surprising. Little imagination is required to envision hypercoagulable lipemic blood (Keys *et al.*[4], O'Brien[7] and Waldron and Duncan[11]) sludging in the coronary vessels and obstructing the flow of nutriment to the heart. A mechanism of this type may in fact be responsible for the diminished oxygen tension and amplitude of contraction of the dog heart during lipemia noted by Sayen and his associates[10]. If similar changes are present in man, they would provide a ready explanation for the phenomenon of post-cibal angina pectoris and perhaps also provide the basis of another provocative test for the presence of asymptomatic coronary heart disease.

Using the ultra-low frequency force ballistocardiograph of Reeves, Jones, and Hefner[8,9], we have studied the pattern and force of ejection of blood from the heart following the ingestion of a fatty meal by persons with and without heart disease. Experience has shown that the records obtained from this ballistocardiographic system usually demonstrate clearly the onset of right and left ventricular ejection, impact of blood on the pulmonary vascular tree and aortic arch, closure of the aortic and pulmonic valves, and small degrees of aortic rigidity (Reeves, Jones and Hefner[8,9]). The amplitude of the ballistic waves is directly proportional to the force applied to the bed throughout the entire frequency range of physiological interest.

Our investigation showed that only one subject displayed any deterioration of myocardial function as measured by the ballistocardiogram. No patient with coronary heart disease manifested any new ballistocardiographic abnormalities after the fatty meal.

Method. Each of 21 subjects was allocated to the "normal" or to the "abnormal" group. The 10 men (ages 19 to 69) in the "normal" group had unexceptional histories, physical examinations, and electrocardiograms. All had normal resting ballistocardiograms save for the 2 oldest subjects, whose records were classified as "borderline" on the basis of a prominent J_D wave and increased duration of the J wave. The 10 men and the one woman (ages 46 to 57) in the "abnormal" group were abnormal on the basis of history, electrocardiogram, and ballistocardiogram.

Ultra-low frequency ballistocardiograms were taken on a table with a natural frequency of 0.2 cycle per second (Reeves, Jones and Hefner[8]). Acceleration was sensed with the electrokinetic device described by

*The opinions expressed in this paper are the personal views of the authors and not necessarily those of the Navy Department.

Elliott, Packard and Kyrazis[2]. The recording sensitivity was adjusted so that 300,000 dynes applied at heart level to the bed loaded with 100 lb. deflected the stylus of a Sanborn Poly-Viso recorder 25 mm. At this setting the same force resulted in a displacement of 17 mm. with 150 lb. loading and 15 mm. with 200 lb. Lead II of the electrocardiogram, the carotid artery pressure pulse, and the phonocardiogram were recorded simultaneously with the ballistocardiogram.

Each of the subjects reported to the laboratory in the morning, having eaten only toast and black coffee since the night previous. Following the control ballistocardiogram, the subjects ate 120 gm. of butterfat in the form of whipped cream sweetened with 5 gm. of sucrose. Three hours later, at a time earlier studies (Beischer and Born[1]) have shown the serum-atherogenic index (Gofman *et al.*[3]) to be at its peak following a test meal of ice cream, a second ballistocardiogram was taken. Records on 4 of the subjects with angina were also taken 5 hours after the meal.

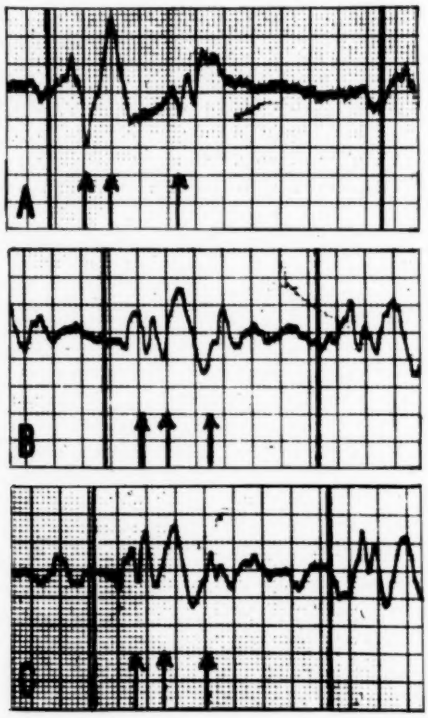

Fig. 1.—*(A)* Ballistocardiogram (50 mm./sec.) of a normal 22-year-old male. The heavy lines are drawn at the time of the electrocardiographic Q waves. The arrows indicate successively the time of onset of the upstroke of the carotid artery pressure pulse, the anacrotic shoulder of the pulse, and the dicrotic notch. Note that the IJ upstroke is synchronous with the first of the arrows, the peak of the J wave with the second, and the L waves with the third. *(B)* Pre-cibal record of subject H.H. The IJ upstroke leads into the formation of a very small J wave. Most of the force is delayed (J_D wave) until after the anacrotic shoulder of the pressure pulse. *(C)* Post-cibal ballistocardiogram of H.H. nearly identical with *(B)*.

All records were coded and were read at the conclusion of the entire experiment by the same observer, who was unacquainted with the subjects' clinical status. Although the records were analyzed in their entirety, particular attention was given to the portion during which the subject held his breath in mid-expiration. Since significant changes in the ballistocardiogram are ordinarily quite large and readily perceived, it was sufficient

TABLE 1.—CARDIAC FUNCTION DURING LIPEMIA

	Subject	*Age*	*History*	*Pre-cibal Angina*	*Electrocardiogram*	*Pre-cibal Ballistocardiogram*	*Post-cibal Ballistocardiogram*	*Post-cibal Angina*
NORMAL	C.P.	39	Normal	None	Normal	Normal	Increased amplitude	No
	R.M.	38	Normal	None	Normal	Normal	Increased amplitude	No
	W.H.	48	Normal	None	Normal	Normal	Slightly diminished amplitude. More force in late systole.	No
	I.J.	42	Alcoholic cirrhosis	None	Normal	Normal	Increased amplitude	No
	C.E.	19	Normal	None	Normal	Normal	Increased amplitude	No
	C.McC.	21	Normal	None	Normal	Normal	Increased amplitude	No
	R.D.	30	Normal	None	Normal	Normal	Unchanged	No
	N.K.	47	Normal	None	Normal	Normal	Unchanged	No
	W.C.	69	Normal	None	Normal	Slight prominence of late systolic forces (J_D wave)	Unchanged	No
	O.N.	53	Normal	None	Normal	Slight prominence of late systolic forces (J_D wave)	Unchanged	No
ABNORMAL	R.C.	52	Anterior myocard. infarct. 3 yrs. ago	1× daily	Anterior infarction	Low amplitude, prominent J_D	Increased amplitude	No
	J.P.	52	Vague chest pains and dyspnea	None	Subendocardial infarction	Low amplitude, prominent J_D	Increased amplitude	No
	C.H.	55	Anterior myocard. infarct. 13 yrs. ago	8× daily	Generally sagging ST segments and inverted T waves	Good amplitude, prominent J_D	Increased amplitude	Yes
	H.H.	54	Posterior myocard. infarct. 2 mo. ago	None	Posterior infarction	Almost all systolic force delayed. J_D the major wave.	Unchanged	No
	C.C.	51	Hypertension	2× daily	Sagging ST in AVL, V5, V6	Low amplitude, prominent J_D	Unchanged	No
	P.F.	49	Hypertension	None	Left axis deviation and Left vent. hypertrophy	Low amplitude, prominent J_D	Increased amplitude	No
	N.B.	57	Angina, 2 yrs.	2× daily	Wide QRS-T angle, low T in V6	Low amplitude, prominent J_D	Unchanged	No
	R.F.	46	Angina, 2 yrs.	1× daily	Wide QRS-T angle, inverted T in many leads	Prominent J_D	Unchanged at 3, incr. amplitude at 5 hours	No
	G.R.	49	Angina, 4 yrs.	1× daily	Low voltage precordial T waves	J_D half of total J wave	Unchanged at 3 & 5 hours	No
	C.M.	48	Angina, 4 yrs.	3× daily	Inversion of T waves after exercise	High H waves, some delay in systolic forces	Increased amplitude at 3 & 5 hours	No
	J.McG.	50	Cong. failure 6 yrs.	1× weekly	Wide QRS-T angle Isoelectric T in many leads	Low amplitude, some delay in systolic forces	Increased amplitude at 3 & 5 hours	No

to describe the resting ballistocardiogram in terms of relative normality, wave amplitude, and wave form and compare the post-cibal record with the initial one in the same qualitative manner.

The significance of the level of serum-cholesterol and serum-lipoprotein in these subjects 3, 5, and 12 hours following the test meal will be reported in another paper.

Results. Table 1 summarizes the findings. Most subjects showed either no change or an unchanged pattern with increased amplitude. Only W.H. showed a change for the worse, and that change was slight. Of the 8 subjects with established angina pectoris, C.H. alone experienced an attack during the 12 hours following the whipped cream. His angina began shortly after the meal and recurred with the same frequency as it did on any usual day.

A typical control and post-absorptive record on a patient with angina (H.H.) is shown in Fig. 1 in comparison with a record of a young person of the same weight.

Discussion. Regardless of the effect of a fatty meal on blood coagulation or of lipemia in diminishing the oxygen tension and amplitude of contraction of the canine myocardium, in man a fat load caused no deterioration in the pattern or force of ejection of blood from the heart under the experimental conditions imposed. Only one person with angina pectoris had an anginal attack during the 12 hours following the test meal; this subject died of his second myocardial infarction 2 months later. The increased amplitude of the post-cibal ballistic waves manifested by some subjects was but a reflection of the known increased cardiac output during a post-absorptive state.

The results of this experiment appear to conflict in some ways with the work of Kuo and Joyner[5]. These investigators administered 0.6 gm. of butterfat per pound of body weight (90.0 gm. for 150 lb. subject) to 7 patients having severe angina pectoris and found that the test meal induced many anginal attacks after 5 hours had elapsed. When the attacks occurred, they were associated with an increase in ballistocardiographic abnormalities registered by the Starr instrument. In at least one instance there was ". . . a progressive deterioration of the systolic ballistic complexes with the rising concentration of the neutral fat content in the circulating blood stream."

Actually, the incompatibility of the two experiments is not so real as it might seem for these reasons: (1) Kuo and Joyner emphasize that their patients were highly selected. All had "severe" coronary heart disease manifested for the most part by angina decubitus[6]. It is possible that they were more severely ill than some of our subjects. On the other hand, if they did have unremitting angina, could they not have had anginal attacks during the test period whether or not they had received the fat?

(2) Normal dogs and those with small myocardial infarctions show an increase in cardiac output and coronary blood flow during lipemia, but measurements decrease in animals with relatively large infarctions (Kuo[6]). Thus, if our subjects are comparable to the dogs with the small infarcts, our findings are easily explained. We cannot accept this interpretation, however, for we know that both subjects C.H. and H.H. had had a large myocardial infarction. When C.H. died 2 months after the experiment, his coronary arteries were nearly completely occluded by atheromatous plaques, and his myocardium showed extensive fibrosis.

(3) The Starr ballistocardiograph, a high frequency system, is distorted by resonant nodes arising when the forc-

ing frequency of the ballistic wave coincides with the natural frequency of the bed; in addition, it is extremely sensitive to variations in the respiratory cycle. The ultra-low frequency force ballistocardiograph is largely free from these defects.

We do not intend by these arguments to dispute the evidence of Kuo and Joyner or to detract from the main thesis of their paper, that selected cases of lipemia-induced angina are relieved by heparin and that certain associated laboratory tests are reverted to normal by this therapy. We conclude only that regardless of the evidence leading one to predict that deterioration of cardiac function might occur during lipemia, no impressive alteration was seen in the force ballistocardiograms of a small group of normal subjects or of patients with known heart disease 3 to 5 hours after a fatty meal.

Summary. Current research suggests that myocardial function might be compromised during lipemia as a result of altered flow-characteristics of blood within the coronary arteries. To test this possibility, ultra-low frequency force ballistocardiograms were taken before a meal of 120 gm. of butterfat and 3 to 5 hours afterwards. No deterioration of myocardial function was found either in normal persons or in patients with heart disease. No attacks of precordial pain were induced in subjects suffering from angina pectoris.

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SUMMARIO IN INTERLINGUA

Le Function Cardiac In Lipemia: Un Studio De Ballistocardiographia A Fortia

Recercas currente pare indicar que le function myocardial es possibilemente compromittite durante lipemia como resultato de alterate characteristicas del fluxo de sanguine intra le arterias coronari. Pro verificar iste possibilitate, ballistocardiogrammas a fortia con ultra-basse frequentias esseva obtenite ante un repasto de 120 g de grassia de butyro e 3 a 5 horas postea. Nulle deterioration del function myocardial esseva constatate, tanto in individuos normal como etiam in patientes con morbo cardiac. Nulle attaccos de dolor precordial resultava in subjectos suffrente de angina de pectore.

SARCOIDOSIS: DISEASE OR SYNDROME*

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A conference on Sarcoidosis, held in 1948 at the National Research Council, after much painstaking deliberation, offered a definition of sarcoidosis. Its report commenced thus: "Sarcoidosis is a disease of unknown etiology, characterized pathologically by epithelioid tubercles, with inconspicuous or no necrosis, occurring in any organ or tissue, and by the frequent presence of refractile or apparently calcified bodies in the giant cells of tubercles." The general clinical features, prognosis, hyperglobulinemia and frequently negative tuberculin reaction were all mentioned. For purposes of the present discussion, the key phrase is "sarcoidosis is a disease of unknown etiology." If this is reckoned with, then perhaps some of the confusion as concerns the relationship between sarcoidosis and certain etiologic agents may be obviated.

A pathologic hallmark is useful for the positive diagnosis of a disease. In the instance of sarcoidosis, the hallmark serves only partially to delineate a syndrome. Tenneson[12], in 1892, first described the histologic features in a patient with lupus pernio and noted the predominance of epithelioid cells and of giant cells. In 1899, Boeck[1] further characterized the histologic features. Subsequent description of the various inclusion bodies, the "para-amyloid" material, and the natural history of the tubercle have rounded out the present knowledge of the pathologic entity known as the sarcoid tubercle. The nonspecificity of the "sarcoid" tubercle has become apparent with further study.

Figure 1, modified after Refvem[11], shows in a schematic fashion the agents that may evoke the sarcoid tubercle. Tuberculoid granulomata are arbitrarily divided into "soft" tubercles, where caseation and necrosis are conspicuous, and "hard" tubercles where necrosis is "inconspicuous or absent." The partial list of known agents producing the "sarcoid" represents a variety of apparently unrelated agents, both living and inanimate. The mechanisms for production of many of the lesions are obscure. It is apparent that many examples listed, such as the tubercle bacillus, do not always evoke the hard tubercle. The inclusion bodies within giant cells of the sarcoid are surely not pathognomonic of sarcoidosis, having been recorded in most of the entities listed. In the consensus of practically all pathologists, however, they do not occur in human tuberculosis (Refvem[11]). Of particular interest in this connection, however, is the observation of Metchnikoff[8] that the Algerian rat responds to infection with human tubercle bacilli with inclusion bodies, highly suggestive of what is now recognized as the Schaumann body.

*Presented at the 70th Annual Meeting of the American Clinical and Climatological Association, Hot Springs, Virginia, October 28, 1957.

Thus, the finding of a "sarcoid" tubercle tells us little as to the underlying disease process and does not permit an exclusive diagnosis of sarcoidosis. Hence, as a pathologic hallmark it leaves much to be desired. On turning to clinical features we find increasing confusion; or perhaps, paradoxically, it is clarification. With better etiologic studies it is becoming apparent that several entities can produce a clinical picture entirely compatible in all respects with Boeck's sarcoidosis.

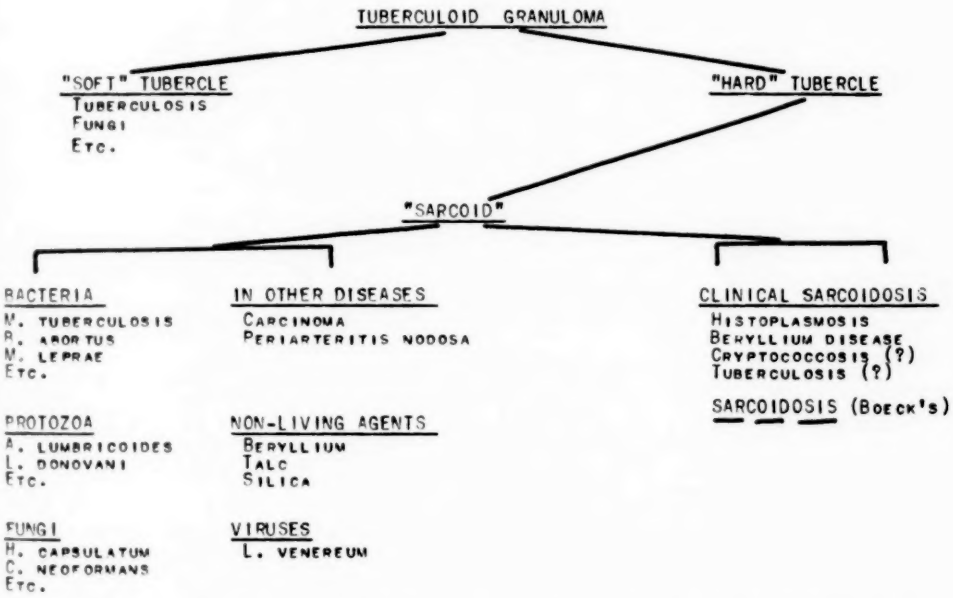

Fig. 1.—Schematic representation of agents capable of producing a sarcoid tubercle. Modified after Refvem[11].

The classical and timely example is the picture resulting from exposure to beryllium or beryllium oxide fumes. We need only to recall that when this syndrome was first recognized it was known popularly as "Salem sarcoid." Initially, there were thought to be many clinical differences between Boeck's sarcoidosis and the pulmonary granulomatosis of beryllium workers. As the latter has been observed for longer periods of time, these differences have diminished both quantitatively and qualitatively (Hardy[4]). There are still some differences, such as ophthalmic lesions and the punched-out osseous lesions of Boeck's sarcoidosis, which have not been recorded in beryllium disease. This becomes of some diagnostic import, but it should be remembered that these two features occur in the minority of patients with sarcoidosis. Furthermore, the huge potato-type pulmonary lymphadenopathy, without bronchial infiltrate, is unknown in beryllium disease. Thus when confronted with a patient having the clinical and pathologic pictures of sarcoidosis, but without the above mentioned features, one must rely on chemical analysis of tissues and on epidemio-

logic features to differentiate between sarcoidosis and beryllium disease.

Another entity that may simulate sarcoidosis clinically and pathologically is histoplasmosis. Pinkerton and Iverson[9] described 3 patients who had clinical and pathologic features of sarcoidosis; indeed, they had been so diagnosed. With special staining technique *H. capsulata* were demonstrated in tissue. Israel and co-workers[6], have described a patient with chronic disseminated histoplasmosis in whom clinical and pathologic features were compatible with sarcoidosis. They raised the question as to whether this was histoplasmosis occurring in a patient with sarcoidosis or the picture of sarcoidosis produced by histoplasmosis. They preferred the latter suggestion, as do I. Again there are clinical differences between the two, but the important point to emphasize is that the disease occasionally produced by *H. capsulata* can mimic that produced by sarcoidosis.

Cryptococcosis has been recently reported to occur in patients with sarcoidosis (Plummer, Symmers and Winner[10]). It is known that *Cryptococcus neoformans* can evoke an histologic picture with a predominance of epithelioid cells and that in some lesions the organisms may not be seen in the center of these epithelioid tubercles. One could speculate that these are not instances of cryptococcosis occurring in a patient with sarcoidosis, but rather that the sarcoidosis picture, both clinically and pathologically, may be produced by the cryptococcus organism in an occasional patient.

Of course, the relationship between tuberculosis and sarcoidosis remains a knotty problem. The controversy has waxed furious, and at times emotional. There are well substantiated instances of patients with sarcoidosis, in whom the tuberculin test is negative and from whom virulent human tubercle bacilli have been recovered (Lees[7]). True, such situations are the exception rather than the rule. Surely it is conceivable and probable that in some patients with sarcoidosis, the picture is produced by the tubercle bacillus.

Brucellosis can produce lesions entirely compatible with those of sarcoidosis (Hoyle, Lawson and Mather[5]). A rare instance of enlarged hilar nodes, presumably resulting from infection with *Br. abortus*, has been noted. It is quite unlikely, however, that the clinical overlap would ever be of sufficient magnitude to make confusion both clinically and pathologically between sarcoidosis and brucellosis.

Granted then that most, if not all, of the pathologic features of the sarcoid tubercle occur in a variety of seemingly unrelated entities and that many of the clinical features of Boeck's sarcoidosis can be found in a few diseases of known etiology, then it becomes necessary to inquire into how these latter diseases can be differentiated. Repeated and careful search for tubercle bacilli, careful mycologic studies, particularly of *H. capsulatum*, may remove an occasional patient with sarcoidosis from the "of unknown etiology" group. Epidemiologic features may be of some help. The significantly higher incidence of Boeck's sarcoidosis among residents of the southeastern United States and among Negroes has been documented (Cummings *et al.*[2], and Gentry, Nitowsky and Michael[3]). Contact with beryllium is always to be sought for. Close proximity to a plant extracting beryllium has been shown adequate for development of the disease. Thus, these clues may at times assume some diagnostic import.

A brief survey of 3 patients will demonstrate some of the points mentioned.

Case Reports. CASE 1. A 33-year-old white female was hospitalized in 1952 because of cough and some dyspnea for one year. At that time scattered fine pulmonary infiltrates and some hilar node enlargement were found (Fig. 2). General physical examination was negative; no lesions were noted in the eyes; there were no bone lesions on roentgenography. Total protein, albumin and globulin values were normal. A biopsy of lung tissue was made and the findings were those of scattered discrete nodular lesions, consisting of a central core of loosely packed epithelioid cells, surrounded by a thin zone of small round cells. Large multinucleated giant cells were seen with only rare ring-shaped inclusion bodies. Comparable findings were noted in the lymph nodes. This, then, is the picture of the "sarcoid" tubercle.

The epidemiologic history of this patient is of considerable interest. She was born in Pittsburgh and lived there for most of her life. Commencing in 1945, for 2 years she was employed as a secretary in a company in Cleveland engaged in the tooling of beryllium, and although most of the time she was in the front office, she did at times go into the dusty work rooms in the back. She made one trip to the main plant where the beryllium was extracted. Beryllium was not found in either her lung biopsy or in her urine. Since the onset of her illness she has gone on to progressive pulmonary fibrosis with some elements of cor pulmonale, and at present has a palpable spleen in addition to the other findings.

Whether this patient has sarcoidosis or beryllium disease is difficult to ascertain. If one sticks strictly to epidemiologic data, then one makes a good story for beryllium intoxication. The fact that there was no beryllium detected in the tissues and in the urine 5 years following her last exposure, by no means rules this out as the cause of her clinical picture and pathologic findings of granulomata. Here then, is an example of the clinical picture compatible with sarcoidosis. Is this true Boeck's sarcoidosis, or is this beryllium disease? Personally, I prefer the latter.

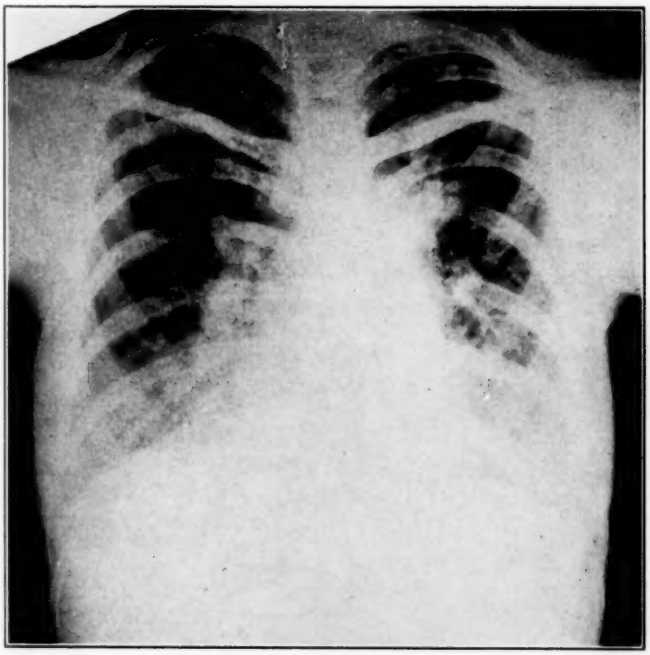

Fig. 2.—Chest film on Case 1 who had the syndrome of sarcoidosis that probably resulted from inhalation of beryllium.

CASE 2. To turn to the more classic "sarcoidosis" let us consider a 27-year-old colored male who was born on a farm in south Georgia. He lived there all his life. Six months

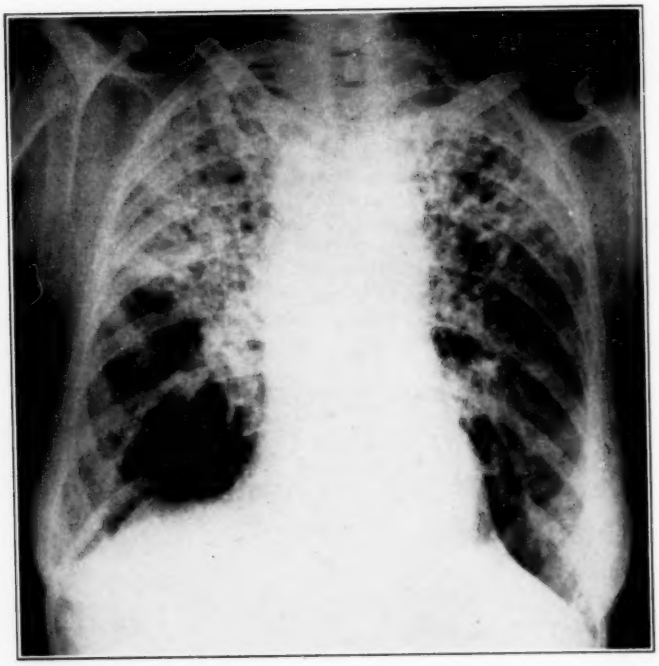

Fig. 3.—Chest film of Case 3 who had chronic pulmonary fibrosis resulting from sarcoidosis.

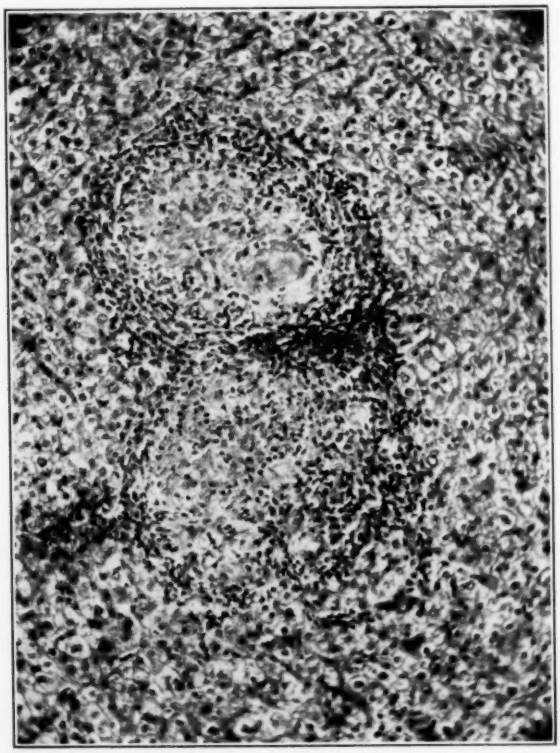

Fig. 4.—Liver biopsy from Case 3. Two sarcoid tubercles are noted. 180 ×.

before admission to the hospital he noted burning of the eyes and lacrimation. There had been some cough, dyspnea and low-grade fever. On physical examination there was enlargement of the lacrimal glands bilaterally, evidence of bilateral uveitis, enlargement of all lymph nodes, a palpable liver and a palpable spleen. Chest film revealed enlarged hilar and right paratracheal nodes. There were miliary infiltrates scattered throughout both lung fields. Tuberculin tests were negative and a Kveim test was positive. A biopsy of the lymph node was compatible with sarcoid. *H. capsulatum* was not found in the tissues. This, then represents what we think of as true Boeck's sarcoidosis. The assumption is that this patient represents the true disease of unknown etiology, sarcoidosis.

CASE 3. Figure 3 shows the chest film of a 56-year-old white female who has had 4 bouts of hemoptysis in the past 3 years. She had extensive pulmonary fibrosis wih bronchiectasis, particularly in the upper portion of her lung fields. Her general physical examination was negative except for a palpable spleen. The serum globulins were elevated. Liver biopsy showed the classical sarcoid tubercles (Fig. 4). This patient was born on a farm in Denmark and migrated to this country some 30 years ago. When confronted with a picture such as this, one would be inclined to say that she did have chronic pulmonary disease, cause undetermined. But by finding the sarcoid tubercles in the liver, the palpable spleen and the hyperglobulinemia, coupled with the epidemiologic pattern, one is forced to say that this patient, too, has sarcoidosis, the disease of unknown etiology.

Summary. A variety of agents, both living and inanimate can evoke the "sarcoid" response pathologically. Moreover, several known agents such as *Histoplasma capsulatum* and beryllium can produce the syndrome of sarcoidosis, both clinically and pathologically. It is reasonable that other pathogenic agents with such propensities will be found. Sarcoidosis, as presently understood, seems to be both disease and syndrome; the vast residue of cases not caused by the known agents may well represent a unity, sarcoidosis, the disease.

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SUMMARIO IN INTERLINGUA

Sarcoidosis: Morbo O Syndrome

Varie agentes, vive e inanimate, pote evocar pathologicamente le responsa "sarcoide." In plus, plure agentes cognoscite, per exemplo *Histoplasma capsulatum* e beryllium, pote producer le syndrome de sarcoidosis, tanto clinica- como etiam pathologicamente. Il pare plausibile expectar que altere pathogenos con tal propensitates va esser trovate. Sarcoidosis, como illo es currentemente comprendite, pare esser si ben un morbo como etiam un syndrome. Il es ben possibile que le vaste residuo de casos non causate per un del agentes cognoscite representa un unitate, le morbo sarcoidosis.

QUANTITATION OF THE MANIFESTATIONS OF RHEUMATOID ARTHRITIS: 7. A NUMERICAL METHOD FOR SUMMING UP TOTAL DEFORMITY

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In this paper we outline a simple method for calculating the total amount of restricted joint motion in a given case of rheumatoid arthritis. For the present we shall refer to the numerical values thus obtained as the "Motion Index." The new index may be viewed as a special adaptation of our previously published "Articular Index"[1] which permits the summation of various joint findings on the basis of accurate measurements of joint size.

The Motion Index is calculated from Table 1, under which is noted the rationale for the calculations. A sample calculation is given in Table 2. The Motion Index expresses total lost motion as a percentage of total possible lost motion, that is, of universal ankylosis. It would, of course, be possible to express it in other terms, such as: sum of lost motion *in the involved joints* only; or per cent of *average lost motion* as found in a large series of unselected cases. But this would necessitate much more complicated methods of calculation.

Goniometric measurement of restricted joint motion is an established and reasonably objective procedure which gives information as to progress towards one of the ultimate goals of therapy: the restoration of normal joint function. A record of lost range of motion in all affected joints is, therefore, desirable as a base-line observation in each new patient. But until now, we have lacked an accurate way of summing up and numerically expressing this important information.

One of the difficulties in measuring joint motion is the amount of time required. The measurement of restricted knuckle motion is especially tedious. But, since the total amount of restricted motion in the fingers is relatively little compared with that of the larger joints, we feel that no great error will result if the observer *estimates by inspection* the average loss of motion in the *affected* finger joints. (Naturally, he should first thoroughly familiarize himself with the normal range of motion in these joints.) Fortunately the time required for the calculation of the Motion Index is relatively little, averaging only 30 seconds per joint in our first series.

In interpreting improvement in range of motion we must remember that while it may occur spontaneously as the activity of the disease subsides, it may also occur when contractures, which are the result of pre-existing rheumatoid activity, are corrected by physical means. Thus increased range of motion does not necessarily indicate improvement in the "activity" of the

disease. Also, although the Motion Index gives a mathematically exact summation of joint function, it must be remembered that the "functional capacity" of the patient in a social sense may be quite a different matter since it will depend on many other factors such as: the location and distribution of joint involvement, the activity of the disease, the patient's courage and determination and type of employment.

In conclusion, we wish to emphasize that the Motion Index is not being advocated for routine use as were the Systemic and Articular Indexes. Rather, it is a mathematical device for summing up range of motion in those situations where such information may be especially useful, such as in carefully conducted, long-range studies of rheumatoid arthritis or in rehabilitation programs.

TABLE 1.—FOR CALCULATING THE "MOTION INDEX"

Each Movable Joint	*Size*	*Range*	*Each Movable Joint*	*Size*	*Range*
Each Terminal I–P Joint	1.4 cm²	90°	Jaw	4	20°
Each Knuckle (M–P and P.I.P.)	4	100	Hips (ab + adduction)	82 cm²	95
First C.M.C. (ab + adduction)	3	35	Knees	104	135
Wrist (A–P only)	15	135	Ankles	35	55
Radio Humeral	26	180	Subastragalar	18	60
Ulnar Humeral	26	145	Bunion	8	55
Shoulder (abduction only)	45	170	First P.I.P.	3	90
Sterno-clavicular	12	56	Each Small Toe, MP Joint	3.7	55
			Each " ", PP "	1	90
			Each " ", TP "	0.56	90

NB. In the case of the First C.M.C. joint, the Wrist, Shoulder and Hip Motion is measured in one plane only as indicated in the table.

The sum of normal degrees of motion *per square centimeter* of joint surface in: 28 knuckles, 24 small toe joints, and 2 of all other peripheral movable joints, is 100,813. For practical purposes we may make the base line 100,000 since the 813 is negligible, so that degrees of motion per square centimeter divided by 1000 for a given patient can be regarded as a percentage of this base line figure.

TABLE 2.—SAMPLE CALCULATION OF THE MOTION INDEX

FORMULA:

$$\%\ \text{lost motion} = \frac{\text{NORMAL} - \text{OBSERVED MOTION} \times \text{JOINT SIZE IN cm}^2}{1000} = \text{INDEX.}$$

	Normal Motion		*Found Motion*		*Lost Motion*		*Joint Size*		
1 wrist	90°	−	60°	= 30°	×	15 cm.		= 450°/cm²
1 knee	120°	−	100°	= 20°	×	104 cm.		= 2080°/cm²
1 knee	120°	−	80°	= 40°	×	104 cm.		= 4160°/cm²
6 knuckles	100°	−	30°	= 70°	×	4 cm.	× 6	= 1680°/cm²
						Sum		= 8370°/cm²

8370 ÷ 1000 = 8.37 = Motion Index

Summary. Goniometric estimation of

range of joint motion is a well-established procedure in many Arthritis Clinics. With a few minute's extra time it is now possible to sum up the total number of degrees lost per area of joint surface and thus arrive at a numerical expression of the total amount of deformity in a given case. This figure is known as the "Motion Index." Tables are given by which these relatively simple calculations (averaging half a minute per joint) can be made. The Motion Index is not advocated for routine use, but rather for special, long-range studies and as a measure of rehabilitation in selected cases.

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SUMMARIO IN INTERLINGUA

Quantitation Del Manifestationes De Arthritis Rheumatoide: 7. Un Methodo Numeric Pro Le Summation Del Deformitate Total

Le estimation goniometric del motion articular es un ben-establite methodo in multe clinicas pro arthriticos. Al costo de pauc minutas de tempore additional, il es nunc possibile summar le numero total del grados de mobilitate perdite per area de superficie articular e obtener assi un expression numeric del quantitate total de deformitate in le caso individual. Iste valor es designate como "Indice de Motion." Es presentate tabulas que permitte le effectuation de iste relativemente simple calculationes (requirente un medie minuta per articulation, minus o plus). Le Indice de Motion non es recommendate al uso routinari sed plus tosto pro studios special a longe vista e como mesura del rehabilitation in casos seligite.

SUMMARIO IN INTERLINGUA

(See page 138 for original article)

Studios Relative Al Lipoproteina Beta Del Sero In Le Bantu Sud-African

1. Le adulte bantu mascule e feminin de Sud-Africa exhibi nivellos seral del lipoproteinas beta del classes S$_f$ 12–100 que es significativemente plus basse que illos de "clinicamente normal" individuos blanc de New York City.

2. Iste constatationes es possibilemente relationate al dieta del bantus.

AN EVALUATION OF MEPROBAMATE IN THE TREATMENT OF VARIOUS RHEUMATIC DISORDERS*

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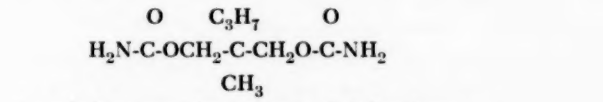
The systematic investigation of the pharmacological properties of substituted ethers of glycerol led to the discovery that some of these substances, among which Myanesin, produced "paralysis with profound muscular relaxation, tranquilization and a sleep-like condition from which the animals could be roused" (Berger and Bradley[2]). In larger doses the animals became ataxic, later paralyzed. Myanesin antagonized the action of strychnine in doses that did not cause paralysis or narcosis. The effect of the drug, later renamed mephenesin, was of short duration because of rapid oxidation. The investigators, Berger and Bradley[2], believed that the curare-like effect of mephenesin was unlikely to be of significance in the production of muscular relaxation by therapeutic doses. Mephenesin appeared to influence favorably the muscular spasm in some spastic and hyperkinetic disorders such as spastic paralysis and Parkinson's disease. It worked better when given intravenously than orally. Its usefulness was sharply limited by its short effect (Berger and Schwartz[4]). In psychiatric patients, too, certain beneficial effects were noted (Schlan and Unna[17]).

Subsequently, attempts were made to prepare similar, but longer-acting drugs. Among these, 2-methyl-2-^{n}-propyl-1,3-propanediol dicarbamate (meprobamate) was unique because it appeared to have muscle relaxant and sedative action of an unusual kind (Berger[1]). Laboratory animals showed evidence of sedation and loss of the righting reflex. No restlessness or excitation were observed as seen in animals treated with barbiturates and other hypnotics. This drug was also more effective than mephenesin when given orally, although it had a longer induction period. It was shown to act on the voluntary muscles only by inhibition of the internuncial circuits. Meprobamate is not broken down in the body, but detoxified by conjugation with glucuronic acid.



2-methyl-2-^{n}-propyl-1,3-propanediol dicarbamate

*Aided by a grant from Wyeth Laboratories, Philadelphia, Pennsylvania; Meprobamate furnished by Wyeth Laboratories for the study under the trade name of Equanil.

Recordings of electrical activity of the brain showed that this compound in low doses increases the voltage and decreases the frequency. This effect is more apparent in recordings from the diencephalon than in those from the cerebral cortex (Hendley, Lynes and Berger[9]). In higher doses all cortical and subcortical recordings showed changes (Berger *et al.*[3]). Unlike reserpine, meprobamate does not cause an increased excretion of 5-hydroxy indoleacetic acid in rats. It antagonizes contractions of the rat colon produced by serotonin or acetylcholine to a lesser degree than either chlorpromazine, reserpine, or benactyzine (Berger *et al.*[3]).

Clinically, meprobamate has been used in psychoses, psychoneuroses, and conditions associated with muscle spasm. Borrus[5,6], Selling[18], and Pennington[15] found it effective in anxiety, tension states, phobias, tension headaches, psychosomatic disorders, insomnia, premenstrual tension, neurodermatitis, and behavior disorders. Lasagna[12] treated chronically ill patients with insomnia with meprobamate. He found it better than a placebo in inducing and maintaining sleep, but not significantly different from phenobarbital. Smith *et al.*[20] believe that the drug is improperly qualified as an ataraxic or tranquilizing drug. According to them, its main clinical usefulness depends upon its muscle relaxant action. They report good to excellent results in 83.3% of 252 patients with rheumatoid spondylitis, fibrositis, cervical root syndrome, mild rheumatoid arthritis, torticollis, muscle spasm of the low back, osteoarthritis of the hips and the knees, chronic gout, and subdeltoid bursitis, as well as in neuritis due to mechanical causes (the spinal root syndrome) (Smith[19]). Scherbel, Schuchter and Harrison[16] found meprobamate helpful in the treatment of rheumatoid arthritis mainly in cases where mild alteration in the patient's affect or in his emotional stability accompanied the arthritis.

Although meprobamate appeared to be harmless in animals as well as in the large majority of patients, some undesirable side effects were noted in a few (1 to 1.5% of all observed patients). Fainting with elevated temperature (Borrus[6] and Selling[18]), drowsiness, often disappearing after the first few days of treatment (Borrus[6] and Lasagna[12]), convulsions under sudden withdrawal, also in a patient who never had a convulsion before (Lasagna[12] and Lemere[13]), have been seen on occasion. Habit formation was believed to be a possible danger (Lemere[13]). Allergic skin rashes (Lasagna[12] and Smith *et al.*[20]), urticaria (Borrus[6] and Selling[18]) in one instance accompanied by swelling of the small joints and generalized pruritus (Kositchek[11]), angioneurotic edema (Selling[18]) have been reported as well. A case of purpura hemorrhagica following a dose of 1200 mg. was described and the author heard of 3 more such cases (Gottlieb[8]). Fever with leukocytosis and marked neutrophilia was seen in one case (Holoubek, Thomas and Segura[10]). Gastric discomfort such as nausea, emesis, activation of ulcer symptoms (Selling[18] and Smith *et al.*[20]), and sluggishness of the small bowel (sic) (Smith *et al.*[20]) also occurred. In a few cases, patients took 20 to 40 gm. in suicide attempts. Gastric lavage and the administration of counter irritants led to no more serious effects than a prolonged period of drowsiness.

Method. Three groups of patients suffering from various rheumatic disorders are included in this study. Group A consisted of 8 such patients studied carefully regarding serum proteins and cholesterol. Group B consisted of 6 patients studied regarding electrolytic alterations, and Group C consisted of 50 pa-

tients of which the majority (26 cases) suffered from psychogenic rheumatism. This larger group was carefully observed from the standpoint of clinical responses. Additional laboratory procedures done on all these patients are described later.

Group A shown in Table 1 consisted of 8 patients whose rheumatic state was complicated by various manifestations of an anxiety neurosis. All these patients had been observed in the outpatient department of the Rochester General Hospital Arthritic Clinic for a period of at least 6 months before beginning meprobamate therapy. All were receiving some type of antirheumatic drug for a period of months before instituting meprobamate therapy with the exception of Case M.G. They were observed clinically. Frequent serum cholesterol and cholesterol ester studies, plasma proteins, and hemograms were performed. No appreciable change was noted in the cholesterol esters or plasma proteins. In only one instance was there a drop in the leukocytes, and that was in the case of J.C. in which the white blood count dropped to 3,850 after the patient had been on 2400 mg. of meprobamate daily for 14 days. The Schilling hemogram was essentially normal in spite of the leukopenia, being as follows: Stab cells 2%, Segmented neutrophils 67%, Lymphocytes 16%, Monocytes 13%, Eosinophils 2%. This patient's monocyte count was elevated before meprobamate therapy and throughout the entire study. It is also interesting that although this patient was continued on this same dose, the following week the white blood count had risen to 4,300. No objective improvement was noted in the joint findings of any of these patients. One patient, F.L., reported that she had less joint pain and was able to walk with less discomfort. However, objectively there was no change.

GROUP B. Six patients representing the following: 1 psychogenic rheumatism, 1 palindromic rheumatism, 1 malum coxae senilis, 1 stage IV rheumatoid arthritis, and 2 osteoarthritis, were studied regarding the following electrolytes while on 1200 mg. of meprobamate daily: potassium, sodium, CO_2, and chlorides. These studies were done weekly starting just before administration of the meprobamate and continuing for a minimum period of 4 weeks. Table 2 shows absence of any abnormalities of electrolytes while on meprobamate therapy. All except 2 patients experienced no clinical benefit. The 2 cases that noted improvement were one suffering from psychogenic rheumatism and the other patient having an early form of malum coxae senilis. The patient suffering from psychogenic rheumatism had complete relief of all joint symptoms and stated that she felt fine. The patient with malum coxae senilis noted less pain and stiffness of her hips. This was true whether salicylates were added to or subtracted from her therapy.

GROUP C. Slightly over 50% (26 cases) of this group represented psychogenic rheumatism. This term denotes musculoskeletal symptoms of a purely functional or psychoneurotic origin without organic lesions. It has also been called psychosomatic rheumatism, psychoneuroendocrine disorder, psychogenic fibrositis, neurotic or hysterical joints, functional muscular disability and psychalgia (Steinberg[21]). The remainder of this group of 50 patients consisted of 6 cases of rheumatoid arthritis, 11 cases of osteoarthritis, and 1 each of malum coxae senilis, protrusio acetabuli, rheumatic heart disease, periarthritis of the shoulders, cardiac neurosis, rheumatoid spondylitis, and menopausal syndrome. This group of patients was treated and observed for a period ranging from one month to one year. Forty cases were treated for at least 3 months. The dose of meprobamate consisted of 200 mg. 3 times daily in 30 patients, 400 mg. 3 times daily in 10 patients, and the remaining 10 cases received variable doses of meprobamate varying from 400 mg. at night only to 400 mg. 4 times daily. All these patients were seen either weekly or bi-weekly. During these periods of observation, the pulse, blood pressure, objective and subjective muscle or joint signs and symptoms, white blood count, platelet, and sedimentation tests were performed. Careful observation was made as to whether or not any untoward signs or symptoms developed as the result of meprobamate therapy. The psychogenic rheumatic group received meprobamate only. The others received some concomitant antirheumatic medication.

Results. By far the best results were obtained in the psychogenic rheumatic group. Out of 26 patients, 22 experienced a satisfactory clinical response. Some of these patients reported feeling well for the first time in years. Six patients with rheumatoid arthritis were treated with meprobamate in a dose of 200 mg. 3 times daily. It may be argued that this dose was insufficient to produce muscle relaxation. However, the reason for this smaller dose was that these patients complained of such

TABLE 1.—EFFECT OF MEPROBAMATE ON CHOLESTEROL, CHOLESTEROL ESTERS, AND PLASMA PROTEINS

Case	*Diagnosis*	*Medication*	*Concomitant Medication*	*Date Cholesterol (mg. per 100 ml.)/ Cholesterol Esters*	*Total Protein gm./100 ml.*	*Serum Albumin gm./100 ml.*	*Serum Globulin gm./100 ml.*	*Remarks*
I.G.	Rheumatoid arthritis stage 2, and anxiety state	Meprobamate 1200 mg./day started 3/13/57	2.5 mg. prednisone daily	2/27/57—356/60%	8.3	4.7	3.6	No relief of joint symptoms, sleeps better. No change in weekly hemogram.
				3/20/57—193/80% (1 week Rx)	7.3	3.5	3.8	
				3/27/57—338/48% (2 weeks Rx)	7.8	4.8	3.0	
				4/ 3/57—303/59% (3 weeks Rx)	6.5	4.0	2.5	
P.D.	Rheumatoid arthritis, stage 2, anxiety, and crying spells	Meprobamate 1200 mg./day started 3/6/57	10 mg. prednisone daily	2/27/57—250/60%	7.4	4.2	3.2	Noticed no joint change or change in anxiety. Meprobamate stopped 4/17/57 because of gingivitis development, cause unknown.
				3/13/57—236/70% (1 week Rx)	7.2	4.1	3.1	
				3/20/57—167/58% (2 weeks Rx)	6.7	3.2	3.5	
				3/27/57—224/63% (3 weeks Rx)	6.6	3.8	2.8	
				4/10/57—217/54% (4 weeks Rx)	6.4	3.3	3.1	
F.L.	Rheumatoid arthritis, stage 3, and anxiety	Meprobamate 1200 mg./day started 3/13/57	10 mg. prednisone daily	3/ 6/57—264/59%	6.7	4.0	2.7	Less joint pain. Able to walk with less discomfort. No change in joint examination.
				3/13/57—217/69% (1 week Rx)	7.0	4.4	2.6	
				4/ 3/57—257/58% (3 weeks Rx)	6.4	3.9	2.5	
				4/10/57—250/57% (4 weeks Rx)	6.4	3.8	2.6	
R.W.	Rheumatoid arthritis, stage 2, and anxiety	Meprobamate 1200 mg./day started 3/13/57	100 mg. phenybutazone daily	3/13/57—162/89%	8.0	4.2	3.8	
				3/20/57—127/58% (1 week Rx)	7.4	3.2	4.7	
M.G.	Rheumatoid arthritis, stage 2, and anxiety	Meprobamate 1200 mg./day started 3/20/57	None until 4/3/57 and then 15 mg. prednisone daily added because of acute exacerbation of rheumatoid arthritis	3/20/57—211/80%	6.9	4.6	2.3	No change in joint or mental status.
				3/27/57—224/69% (1 week Rx)	6.5	4.7	1.8	
				4/ 3/57—264/66% (2 weeks Rx)	6.5	4.0	2.5	
				4/17/57—244/66% (4 weeks Rx)	6.1	3.8	2.3	
				5/ 1/57—212/74% (6 weeks Rx)	6.5	4.2	2.3	
J.C.	Osteoarthritis and marked anxiety	Meprobamate 1200 mg./day started 4/3/57 and increased to 1600 mg. 4/10/57 and 2400 mg. 5/1/57	300 mg. Butazolidin daily	4/ 3/57—194/83%	6.7	3.8	2.9	No relief. WBC down to 3850 on 5/15/57 and 4300 on 5/22/57. No drop in % of granulocytes.
				4/10/57—157/64% (1 week Rx)	6.6	3.6	3.0	
				4/23/57—226/77% (3 weeks Rx)	7.8	4.1	3.7	
				5/15/57—223/50% (6 weeks Rx)	7.1	3.9	3.2	
M.B.	Osteoarthritis	Meprobamate 1200 mg./day	100 mg. Butazolidin daily	3/27/57—300/56%	6.7	4.6	2.1	
				4/ 3/57—264/59%	6.0	3.6	2.4	
				4/10/57—264/58%	6.0	3.7	2.3	
				4/24/57—312/70%	6.8	4.3	2.5	
A.K.	Osteoarthritis	Meprobamate 1200 mg./day	100 mg. Butazolidin daily	3/27/57—328/47%	7.1	4.3	2.9	
				4/ 3/57—337/52%	6.8	4.1	2.7	
				4/24/57—348/59%	8.1	4.6	3.5	

somnolence that larger doses were not possible. Clinical benefit in 2 patients was more concerned with less nervousness than with less muscle spasm or joint relief. None of 11 patients with osteoarthritis noted relief from the arthritis *per se* or from any muscle stiffness or jelling. Three stated they were less nervous and slept better.

organic joint disease associated with psychoneurosis indicates that 7 patients out of a group of 24 noted relief of these symptoms.

Untoward Reactions. The most troublesome untoward symptom noted from meprobamate therapy was somnolence. In many instances the dose had to be decreased because the pa-

TABLE 2.—EFFECT OF MEPROBAMATE ON ELECTROLYTES

Case	*Diagnosis*	*Meprobamate*	*Other Medication*	*Date*	*Na*	*K*	*Cl*	*CO_2*
J.L.	Psychogenic rheumatism	1200 mg. daily	None	*3/13/57	150	4.3		
				4/ 3/57	140	5.6	109	23
				4/17/57			113	22
				5/ 1/57	145	4.6	111	24
P.P.	Palindromic rheumatism	1200 mg. daily	30 mg. prednisone daily, gold weekly	*4/ 3/57	144	4.6	109	25
				4/10/57	148	4.3	105	24
				4/17/57	152	4.6	111	23
P.L.	Malum coxæ senilis, early	1200 mg. daily	None	*4/ 3/57	137	3.9	112	27
				4/10/57	146	4.7	111	21
				4/17/57	144	4.5	114	20
				4/23/57	152	3.9	111	22
				5/ 1/57	146	4.3	113	21
H.M.	Rheumatoid arthritis, stage 4	1200 mg. daily	15 mg. prednisone daily	*5/ 1/57	145	4.6	111	19
				5/15/57	141	4.9	109	21
A.K.	Osteoarthritis	1200 mg. daily	100 mg. Butazolidin daily	*3/20/57	147	4.3	107	24
				3/27/57	141	4.9	104	22
				4/ 3/57	140	4.5	112	26
				4/24/57	146	4.4	108	23
M.B.	Osteoarthritis	1200 mg. daily	None	*3/27/57	144	5.1	108	23
				4/ 3/57	141	4.9	110	22
				4/24/57	149	4.3	113	23

* Initial determination made in each case before starting meprobamate therapy.

In the group with miscellaneous disorders, the patient with rheumatoid spondylitis noted much less muscle stiffness of his back. His insomnia also was relieved by meprobamate 400 mg. 3 times daily. The patient with a cardiac neurosis noticing relief of anxiety also had mild osteoarthritis. The patient with menopausal symptoms also had mild osteoarthritis, but the menopausal symptoms were the outstanding feature.

An analysis of the patients who had

tients stated that they would fall asleep at the dinner table or while engaged in conversation. Some degree of this was noted in 40 cases. Dizziness was noted in 5 patients. One patient noticed gastric distress severe enough to stop the medication. One patient's gait was so unsteady that the medication had to be stopped. Three patients stated, "My head feels big, and I am unable to wake up." One patient developed a skin rash, but this patient was also receiving Butazolidin therapy, and it

was difficult to determine which drug caused the rash. No change in the pulse or blood pressure was noted in the entire group. In no instance of organic joint disease was any clinical benefit obtained by adding the meprobamate as regards the sedimentation rate or joint swelling. A leukopenia of 3,850 without suppression of granulocytes appeared in one patient after taking 2,400 mg. of meprobamate daily for 2 weeks. The leukocyte count rose to 4,300 the following week while the patient was still on the same dose. Recently (Meyer, Heeve and Bertscher[14]) a case of fatal aplastic anemia was reported in a 28-year-old woman who had taken 1,200 mg. of meprobamate daily for 8 days. However, it is to be noted that this patient may have had some type of blood dyscrasia before starting this drug since the protocol stated that "The patient stated that she always bruised easily." We have noted no evidence of addiction in any of these people; but, Ewing and Fullitone[7] noted withdrawal symptoms in a 32-year-old man who had taken 4000 to 8000 mg. of meprobamate daily for 3 months. We find this situation most unusual because none of our patients could possibly stay awake on such high dosage.

Summary. The effect of meprobamate therapy was studied in three groups of patients suffering from various rheumatic disorders. In Group A, consisting of 8 patients, no appreciable change was noted in the cholesterol esters or plasma proteins while under meprobamate therapy. A leukopenia of 3,850 developed in one patient after having been on 2,400 mg. of the drug daily for 14 days. No objective improvement was noted in the joint findings of any of these patients. In Group B, consisting of 6 patients, no abnormalities were found in the electrolytes while under 1200 mg. of meprobamate treatment daily. Group C consisted of 50 cases of which 26 cases represented patients with psychogenic rheumatism. Of these 26 patients 22 experienced a satisfactory clinical response. Some of these patients reported feeling well for the first time in years.

Meprobamate is a valuable drug for the treatment of psychogenic rheumatism. Its effect on organic joint disease was practically nil in the series here reported. Side effects were so minor as to place this medication within a safety range rarely enjoyed by any other newer drugs now being used in rheumatic disorders.

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SUMMARIO IN INTERLINGUA

Un Evalutation De Meprobamato In Le Tractamento De Varie Disordines Rheumatic

Le effecto de therapias a meprobamato esseva studiate in tres gruppos de patientes qui suffreva con varie disordines rheumatic. In Gruppo A, consistente de 8 patientes, nulle appreciabile alteration esseva notate in le esteres cholesterolic o le proteinas del plasma durante le curso de therapia a meprobamato. Un leucopenia de 3.850 se disveloppava in un del patientes post que ille habeva recipite 2.400 mg del droga per die durante 14 dies. Nulle melioration objective esseva constatate quanto al stato del articulationes in ulle de iste patientes. In Gruppo B, consistente de 6 patientes, nulle anormalitates esseva notate in le electrolytos durante le administration de 1.200 mg de meprobamato per die. Gruppo C consisteva de 50 patientes. Vinti-sex de illes suffreva de rheumatismo psychogene. Inter iste 26 patientes, 22 habeva un satisfacente responsa clinic. Certes de illes reportava le prime sensation de ben-esser depost plure annos.

Meprobamato es un droga de valor in le tractamento de rheumatismo psychogene. Su effecto in casos de organic morbo articular esseva practicamente absente in le series hic reportate. Le effectos lateral esseva si nettemente minor que on pote asserer que iste droga occupa un rango de securitate rarmente attribuibile a un droga del typo del plus recente compositos nunc in uso in le tractamento de disordines rheumatic.

USE OF CHLOROTHIAZIDE IN THE TREATMENT OF EDEMA

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Chlorothiazide,* a new diuretic agent recently described by Russo, Baer, Noll and Beyer[1], has been shown by these investigators to have an action similar to that of the mercurial diuretics, in promoting sodium, chloride, and potassium excretion by blocking tubular reabsorption. Although pharmacologically it acts, in some preparations, as a carbonic acid anhydrase inhibitor, it does not have this effect on the kidney in ordinary doses: that is, it does not increase bicarbonate excretion, or produce an alkaline urine with systemic acidosis. Chemically, chlorothiazide is a new compound, 6-chloro-7-sulfanyl-1,2,4,benzothiadiazine-1,1-dioxide.

Clinical Material. The present report describes a preliminary study with the use of chlorothiazide, in therapeutic doses by mouth, in the treatment of various types of resistant clinical edema.

Twenty-seven courses of therapy have been given to 13 patients, and the diuretic response noted by change in body weight. The clinical diagnoses were as follows: 3, rheumatic heart disease; 3, arteriosclerotic heart disease; 2, hypertensive cardiovascular disease; one, cor pulmonale and arteriosclerotic heart disease combined; 2, Laennec's cirrhosis; one, nephrosis; one, heart disease of unknown etiology. Most of the cases were in advanced congestive failure, several were resistant to other diuretic agents. All patients were in the hospital wards, on a strict salt-poor regimen, receiving supportive therapy, other than diuretics, as indicated. A control period in the hospital, to establish a base line of unchanging, or increasing, body weight, was carried out in most instances. In several, repeated courses of therapy were given, with body weight tending to rise between courses.

Two additional patients, with longstanding chronic pulmonary disease and cor pulmonale, in very severe pulmonary failure, requiring respiratory aid either with the tank or positive pressure respirator, were given courses of chlorothiazide to study the effects on blood gases and electrolytes.

The usual dosage of chlorothiazide was 2 gm. daily given in four divided doses. A few courses were on dosage schedules of 1 gm., and a few at 4 gm. daily.

Results. The results are shown in Table 1. Seven of the 10 cardiac patients had satisfactory diuresis on chlorothiazide; 3 did not. Two of the latter were also unresponsive to mercurial diuretics; the third received inadequate trial on chlorothiazide, but responded well to Thiomerin and ammonium chloride. The nature of the response to chlorothiazide in those that responded, was a steady and progressive loss of weight, extending over many days.

One of the patients with cirrhosis had an excellent response, the other slight. The nephrotic patient was resistant to all therapy.

In Table 2 are given the measure-

*The chlorothiazide used in this study was provided through the kindness of Dr. John R. Beem of Merck Sharp & Dohme Division of Merck & Co., Inc., West Point, Pa.

TABLE 1.—DIURETIC ACTION OF CHLOROTHIAZIDE

Patient Sex, Age, Diagnosis	*Date*	*Dose per Day Grams*	*Duration of Treatment Days*	*Weight Start lbs.*	*Weight Finish lbs.*	*Total Change lbs.*	*Other Diuretics Effective?*
J. diB.	3/17	2	4	124	118	6	No (merc. and others)
m., 50	3/27	2	10	122	116	6	—
R.H.D.	4/9	4	6	121	112	9	No
Edema +++							
H.G.	3/11	1	4	161	156	5	—
m., 49	3/19	2	4	154	148	6	—
A.S.H.D.	3/28	2	6	148	144	4	—
A.F. Edema ++	4/3	4	9	144	141	3	No
W.M.	3/20	2	3	157	153	4	Yes (merc.)
m., 50	3/28	2	6	157	154	3	—
H.C.V.D.	4/3	4	4	153	153	0	No
Edema ±							
S.B.	5/14	2	4	146	138	8	Slight (merc. and
m., 46	5/23	2	32	137	115	22	Diamox)
Cirrhosis							
Edema ++							
J.M.	3/9	1	4	125	116	9	—
m., 77	3/17	2	4	116	114	2	—
Cor. pulm.							
A.S.H.D.							
Edema +							
H.W.	3/12	1	5	158	155	3	
m., 71	3/17	Mercuhydrin gave small added diuresis					
A.S.H.D.	3/21	Died					
Edema ++++							
S.S.	3/13	2	5	168	168	0	Nothing effective
m., 77							
Nephrosis							
Edema ++++							
G.S.	4/7	2	4	127	122	5	No (merc.)
m., 58	4/16	4	10	127	120	7	—
R.H.D.							
Edema +++							
L.W.	3/16	2	4	203	188	15	Yes (merc.)
m., 40							
Unknown H.D.							
Edema ++							
J.N.	4/3	2	5	158	143	15	No (merc.)
m., 70	4/23	2	6	146	140	6	No (merc.)
A.S.H.D., A.S.							
Heart block							
Edema ++							
T.N.	4/7	2	4	131	124	7	—
m., 60	4/16	4	6	127	125	2	No (merc.)
R.H.D.							
Edema +++							
A.S.	5/26	2	2	225	223	2	Yes (Thiomerin)
m., 55	6/10	2	2	200	197	3	"
H.C.V.D.							
Edema ++++							
C.H.	5/21	2	4	167	162	5	No (merc.)
m., 46	6/3	2	23	170	165	5	No (merc.)
Cirrhosis							
Edema +							

R.H.D. = rheumatic heart disease.
A.S.H.D. = arteriosclerotic heart disease.
A.F. = atrial fibrillation.
H.C.V.D. = hypertensive cardiovascular disease.

ments of blood electrolytes, in 11 patients. In 5, the serum potassium levels dropped transiently below 3.0 mEq. during chlorothiazide therapy. No clinical or electrocardiographic signs of hypopotassemia were observed. It may be noted that in one patient, S.B., serum potassium also fell to 2.7 mEq. after mercurial and Diamox administration. In one patient, the serum uric acid level was found to be 12.1 mg. per 100 ml., three days after starting chlorothiazide, but the uric acid level dropped even during continuation of treatment. There were no clinical symptoms.

In general, chlorothiazide in all doses used appeared to be completely free from clinical toxic side effects.

In Table 3 the results of rather pro-

TABLE 2.—EFFECTS OF CHLOROTHIAZIDE ON BLOOD ELECTROLYTE VALUES

Patient	*Date*	*Chloro gm./day*	*No. Days on Chloro.*	*Na mEq.*	*K mEq.*	*Cl mEq.*	*CO_2 mEq.*
J. diB.	3/9	0	0	131	4.1	102	19.1
	3/28	2	7	128	2.3	90	24.4
H.G.	3/21	0	0	143	3.3	108	21.7
	4/5	2	9	126	3.2	102	25.2
W.M.	3/7	0	0	135	4.6	102	20.8
	3/21	2	2	140	3.2	98	27.8
	4/4	2	8	132	2.7	93	24.4
S.B.	4/30	0	0	140	3.4	95	22.6
	4/30–5/6	on merc. and Diamox for 8 days					
	5/9	0	0	134	2.7	104	20.9
	5/16	2	3	132	2.7	102	27.6
	5/28	2	6	130	2.0	85	27.0
	6/4	2	13	135	3.2	102	25.0
	6/5–6/12	Chloro 2.0 gm. plus KCl 1.5 gm.					
	6/13			132	2.9	94	23.0
	6/13–6/20	Chloro 2.0 gm. plus KCl 3.0 gm.					
	6/20			127	2.7	98	25.0
	6/24	0	0	142	4.1	104	—
J.M.	3/8	0	0	150	4.4	97	—
	3/13	1	4	133	4.1	90	27.0
H.W.	3/8	0	0	139	4.9	94	26.0
	3/14	1	3	137	4.0	92	25.0
G.S.	4/2	0	0	143	4.2	101	21.7
	4/22	4	7	139	2.9	98	28.4
L.W.	3/16	2	3				12.1
	3/20	2	5	Serum uric acid mg./100			8.6
	3/25	0	0				5.4
T.N.	4/22	4	6	139	3.6	101	30.2
A.S.	5/28	2	2	140	4.3	96	21.0
	5/28–6/6	on Thiomerin 2/ml. every 3 days					
	6/6	0	0	140	4.3	94	24.0
C.H.	6/6	2	4	141	3.4	95	26.0
	6/11	2	9	138	2.9	97	25.0
	6/13–6/16	Chloro 2.0 gm. plus KCl 1.8 gm.					
	6/18	2	16	136	2.6	100	21.6

longed chlorothiazide administration in 2 cases of advanced cor pulmonale are recorded. One of these cases (W.G.) had variable but usually slight clinical edema; the other (A.Y.) was edema-free. It will be seen that there were no consistent or definite changes in blood electrolytes or blood gas values that could be attributed to the effects of chlorothiazide, except for a moderate lowering of serum potassium and rise in arterial pH's in one case.

TABLE 3.—COR PULMONALE. INTRACTABLE CARDIORESPIRATORY FAILURE. EFFECTS OF CHLOROTHIAZIDE ON ELECTROLYTES AND BLOOD GASES

Patient	*Date*	*Chloro gm./day*	*Na mEq.*	*K mEq.*	*Cl mEq.*	*pCO_2 mm.*	*Art. pHs*	*Hct.*	*Art. O_2 sat.%*
A.Y.	1/2/57	0	135	4.8	95	71	7.32	52	63
	3/26	0	—	—	—	61	7.34	49	78
	3/30–4/19	2	—	—	—	62	7.32	53	85
	4/26	0	140	3.7	93	64	7.36	52	72
	4/30–5/3	4	149	4.2	90	57	7.38	58	81
W.G.	3/5	on Diamox	131	4.8	93	51	7.37	53	89
	4/7–4/18	2	—	—	—	—	—	—	—
	4/16	2	139	2.7	90	63	7.38	48	80
	4/22	0	143	4.1	95	—	—	—	—
	5/17	0	138	4.9	85	58	7.37	45	87
	5/20–6/21	4	—	—	—	—	—	—	—
	6/10	4	141	3.5	98	52	7.45	47	82
	6/17	4	—	—	—	56	7.42	45	83

Discussion. These were all cases of resistant edema, several, as indicated in Table 1, having become refractory to the mercurial and other diuretics. Though the group is small, the favorable responses in most of the patients in this series suggest that chlorothiadiazide is an effective oral diuretic. The only unfavorable side effect, a lowering of serum potassium levels, is, of course, an effect inherent in the saluretic action of the drug. Obviously potassium levels must be watched closely in the clinical use of the drug. Since the writing of this paper, the present investigators have been employing chlorothiazide successfully in both hospital and outpatient cases on a weekly schedule of intermittent therapy, 4 days on and 3 days off.

Summary. Chlorothiazide, a new oral diuretic, has been used in 13 cases of resistant edema, several of them refractory to other agents. Diuresis occurred in 7 of 10 cardiac patients and in 2 cases of cirrhosis with edema. No unfavorable side effects were noted, except for a transient and asymptomatic lowering of serum potassium levels in 5 cases.

REFERENCE

1. **Russo, H. F., Baer, J. E., Noll, R. M.,** and **Beyer, K. H.:** Fed. Proc., **16,** 333, 1957.

SUMMARIO IN INTERLINGUA

Le Uso De Chlorothiazido In Le Tractamento De Edema

Chlorothiazido, un nove diuretico oral, esseva usate in 13 casos de edema resistente, incluse plures que esseva resistente a altere agentes. Diurese occurreva in 7 ex 10 patientes cardiac e in 2 casos de cirrhosis con edema. Nulle adverse effectos lateral esseva notate, excepte un transiente e asymptomatic reduction del nivellos seral de kalium in 5 casos.

DICHLORPHENAMIDE AS A DIURETIC AGENT

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The continued search for effective diuretic agents evolves from the readily apparent shortcomings of agents presently available for clinical use. Dichlorphenamide (1,3-disulfamyl-4,5-dichlorobenzene) is a relatively simple disulfamyl compound that has some unusual and striking differences from the carbonic anhydrase inhibitors which are currently available. This report deals with the results of observations in man and dogs following the administration of dichlorphenamide.†

Materials and Methods. A. LABORATORY OBSERVATIONS. The acute diuretic response to dichlorphenamide was studied in 32 dogs that were not hydrated with water. These animals were taken from their cages on the morning of the study, anesthetized with 30 mg. of pentobarbital, and then catheterized. The control observations were made over three 20-minute urine collection periods. Then, the drug was given intravenously. Eight dogs received 10 mg./kg. of dichlorphenamide, eight received 2 mg./kg., eight received 1 mg./kg., and eight received 0.5 mg./kg. Observations were then made continuously for the next 4 hours using 20-minute urine collection periods. Urine volume and sodium and potassium excretion rates were studied.

B. CLINICAL OBSERVATIONS. The technique of this study has been described previously (Ford, Spurr and Moyer[2]). Briefly, 20 male patients with equivalent degree of well controlled congestive heart failure are the subjects of the study of this drug. These patients are maintained in an air-conditioned metabolic ward under the observation of trained personnel. With the exception of diuretic agents, all medications required for control of their heart failure are continued throughout the study. The patients are allowed to be ambulatory about the metabolic ward. The sodium content of each patient's diet is exactly 50 mEq. per 24 hours. The patients drink 3000 ml. of distilled water every day. They remain on this diet until each patient excretes a constant amount of sodium, which

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†Trade name: Daranide.

TABLE 1.—EFFECT OF DICHLORPHENAMIDE ON WATER AND ELECTROLYTE EXCRETION—HIGH DOSES

Dog No.	*Urine Volume ml./min.*							*Urine Sodium μEq./min.*							*Urine Potassium μEq./min.*							Dog Wt. kg.
	C	D_1	D_2	D_3	D_4	D_5	D_6	*C*	D_1	D_2	D_3	D_4	D_5	D_6	*C*	D_1	D_2	D_3	D_4	D_5	D_6	
10 mg./kg. of Dichlorphenamide intravenously																						
1	0.2	1.0	1.0	0.8	0.5	0.3	0.4	10	200	220	168	88	45	32	10	46	49	35	15	12	13	11.0
2	0.2	1.0	1.0	0.7	0.6	0.4	0.4	24	220	255	168	112	59	41	12	22	21	12	29	31	30	9.0
3	0.2	1.6	1.8	1.3	1.2	1.1	0.6	10	315	330	260	288	225	128	10	64	56	40	48	40	44	14.0
4	0.2	0.7	1.1	0.6	0.6	0.5	0.7	13	75	95	63	53	55	75	5	35	63	45	35	27	41	8.0
5	0.2	1.6	1.1	0.5	0.1	0.1	0.2	38	205	165	68	7	5	6	7	27	23	11	2	1	1	7.0
6	0.2	1.0	0.6	0.6	0.6	0.5	0.4	10	205	135	143	117	103	70	2	38	19	22	25	24	17	9.0
7	0.1	0.1	0.1	0.1	0.2	0.7	0.2	10	8	10	9	13	152	31	1	1	1	1	2	55	8	12.0
8	0.2	1.6	0.9	0.8	0.5	0.4	0.4	28	150	180	150	103	75	70	7	116	60	56	49	35	24	11.0
Mean	0.2	1.1	1.0	0.7	0.5	0.5	0.4	18	172	174	129	98	90	57	7	44	37	28	26	28	22	10.1
% of Control		550	500	350	250	250	200		956	967	717	544	500	317		629	529	400	371	400	314	
P Value		.01	.01	.01	.01	.05	.01		.01	.01	.01	.05	.05	.05		.05	.01	.05	.01	.05	.05	
2 mg./kg. of Dichlorphenamide intravenously																						
1	0.2	0.3	0.3	0.4	0.5	0.4	0.4	3	36	45	57	88	65	68	3	12	16	19	29	24	14	11.0
2	0.2	0.5	0.4	0.5	0.7	0.4	0.4	5	40	40	53	50	20	23	8	19	13	15	13	7	8	8.0
3	0.1	0.2	0.6	0.5	0.4	0.4	0.3	4	10	75	45	38	30	18	2	4	72	34	25	25	14	8.0
4	0.2	1.0	0.6	0.6	0.4	0.4	0.4	9	215	105	130	77	80	75	3	55	27	35	16	20	21	12.0
5	0.3	0.8	0.5	0.5	0.3	0.3	0.3	11	185	85	48	2	1	2	4	18	7	15	5	10	10	11.0
6	0.3	1.0	0.6	0.3	0.3	0.3	0.3	3	30	25	9	2	1	1	2	64	34	17	11	8	6	9.0
7	0.2	1.0	0.5	0.6	0.5	0.5	0.5	10	185	105	125	127	110	85	13	25	8	11	17	25	21	13.0
8	0.2	0.5	0.3	0.4	0.3	0.3	0.3	4	85	41	61	41	38	23	4	40	20	22	11	21	20	12.0
Mean	0.2	0.7	0.5	0.5	0.4	0.4	0.4	6	98	65	66	53	43	37	5	30	25	21	16	18	14	10.5
% of Control		350	250	250	200	200	200		1633	1083	1100	883	717	617		600	500	420	320	360	280	
P Value		.01	.001	.001	.05	.01	.01		.05	.001	.01	.05	.30	.05		.05	.05	.01	.05	.01	.01	

TABLE 2.—EFFECT OF DICHLORPHENAMIDE ON WATER AND ELECTROLYTE EXCRETION—LOW DOSES

Dog No.	Urine Volume ml./min.							Urine Sodium μEq./min.							Urine Potassium μEq./min.							Dog Wt. kg.
	C	D_1	D_2	D_3	D_4	D_5	D_6	C	D_1	D_2	D_3	D_4	D_5	D_6	C	D_1	D_2	D_3	D_4	D_5	D_6	
1 mg./kg. of Dichlorphenamide intravenously																						
1	0.2	0.4	0.3	0.3	0.2	0.2	0.2	10	55	33	54	61	62	43	4	34	18	21	11	10	8	13.0
2	0.2	0.7	0.6	0.5	0.3	0.2	0.2	3	77	84	77	61	30	46	3	30	32	21	14	10	21	9.0
3	0.1	0.3	0.3	0.3	0.3	0.2	0.2	5	45	50	53	34	29	13	4	28	21	17	17	19	10	12.0
4	0.1	0.6	0.5	0.3	0.3	0.2	0.3	5	105	90	60	28	20	53	7	45	37	22	15	15	23	12.0
5	0.2	0.5	0.4	0.4	0.3	0.2	0.3	12	40	30	12	7	8	5	24	22	23	14	5	10	10	10.0
6	0.3	0.9	0.7	1.3	1.5	0.5	0.2	30	150	110	200	203	40	13	8	16	11	29	18	11	3	13.0
7	0.1	0.2	0.2	0.4	1.0	0.8	0.5	7	7	11	36	220	190	95	1	1	2	8	33	39	41	8.0
8	0.1	0.5	0.5	0.4	0.4	0.3	0.3	6	75	50	50	38	30	27	4	30	22	20	11	8	11	12.0
Mean	0.2	0.5	0.4	0.5	0.5	0.3	0.3	10	69	57	68	82	51	37	7	26	21	19	16	15	16	11.1
% of Control		250	200	250	250	150	150		690	570	680	820	510	370		371	300	271	229	214	229	
P Value		.001	.001	.05	.05	.05	.20		.01	.01	.05	.05	.10	.10		.01	.05	.05	.20	.10	.20	
0.5 mg./kg. of Dichlorphenamide intravenously																						
1	0.2	0.2	0.2	0.2	0.2	0.2	0.2	17	36	26	12	11	16	13	20	12	16	9	13	11	9	13.0
2	0.3	0.9	0.8	0.6	0.4	0.4	0.4	4	73	64	50	25	15	6	6	47	36	28	15	18	11	13.0
3	0.3	0.6	0.4	0.4	0.3	0.2	0.2	3	51	40	39	29	17	14	14	37	28	26	23	14	14	11.0
4	0.2	0.5	0.4	0.3	0.2	0.2	0.2	16	80	65	48	32	20	19	4	17	13	10	8	11	10	11.0
5	0.3	0.7	0.4	0.3	0.2	0.2	0.3	53	115	85	50	27	15	25	14	20	18	12	11	25	25	10.0
6	0.4	0.6	0.4	0.2	0.2	0.2	0.1	6	65	55	28	24	9	9	22	30	27	17	12	7	6	8.0
7	0.2	0.5	0.2	0.2	0.2	0.2	0.2	13	16	31	33	29	22	24	13	26	13	11	13	11	13	8.0
8	0.4	1.0	0.7	0.5	0.5	0.5	0.4	45	140	90	50	43	35	40	7	20	10	8	13	18	13	16.0
Mean	0.3	0.6	0.4	0.3	0.3	0.3	0.3	20	72	57	39	30	19	19	13	26	20	15	14	14	13	11.3
% of Control		200	133	100	100	100	100		360	290	195	150	95	95		200	154	115	108	108	100	
P Value		.01	.05	.10	.50	.50	.50		.01	.001	.05	.30	.50	.50		.05	.40	.50	.50	.05	.50	

Key to abbreviations:
- C = Control, average of three 20-minute periods
- D_1 = Observations made 30 minutes after drug administration, average of two 20-minute periods
- D_2 = Observations made 1 hour after drug administration, average of two 20-minute periods
- D_3 = Observations made 1½ hours after drug administration, average of two 20-minute periods
- D_4 = Observations made 2 hours after drug administration, average of two 20-minute periods
- D_5 = Observations made 3 hours after drug administration, average of two 20-minute periods
- D_6 = Observations made 4 hours after drug administration, average of two 20-minute periods

approximates 90% (45 mEq./24 hrs.) of their dietary sodium. The diuretic agent to be tested is then administered. Before the administration of the next dose of the diuretic agent, several days (3 to 5) are allowed for the patient to regain his body weight by the restoration of sodium and water stores.

Each patient is weighed before breakfast and after voiding. Urine is collected in 24-hour periods and analyzed for sodium, potassium, chloride, volume, and creatinine (as a test of the accuracy of the collection). Other routine studies include plasma electrolytes, electrocardiograms, and chest roentgenograms on each patient.

A complete electrolyte excretion pattern was obtained on 2 patients receiving dichlorphenamide. Each patient drank 3000 ml. of distilled water per day. This was allotted fractionally to assure a constant water intake throughout the day. Urine was collected under oil in six periods per 24 hours (three 2-hour periods and three 6-hour periods). The specimens were analyzed for sodium, potassium, chloride, phosphate, titratable acidity, ammonia, bicarbonate, total solutes, and volume. Dichlorphenamide was administered orally to one patient twice at a dose of 50 mg. every 12 hours and to the second patient as a single dose of 500 mg.

Dosage response relationships were determined with this agent. Observations on this drug were then compared to currently available diuretic agents. Dichlorphenamide was given orally in single doses starting with a dose of 50 mg., progressively increasing the dose (100, 200, 500, 1000 mg.) until it was seen that a dose in excess of 200 mg. produced symptoms of gastrointestinal and central nervous system toxicity in over 25% of the patients without any further augmentation of sodium excretion. Since doses of 50 and 100 mg. produced optimum sodium response without toxicity, the bioassay was limited to these two dosages.

The effect of chronic administration was studied by giving 50 mg. twice daily for 5 days to 2 patients. Quantitative urine sodium excretion rate was determined daily. Serum electrolytes (BUN, Na, K, Cl, CO_2, Hct.) were obtained in the control state and on the second and fifth day of drug administration.

Results. A. LABORATORY OBSERVATIONS. There was a significant increase in urine volume within 30 minutes after the administration of 0.5 mg./kg. of dichlorphenamide, but within 1½ hours this diuretic effect was lost. However, with doses of 2 mg./kg. and 10 mg./kg., the diuretic response continued over a period of 4 hours.

As with the water excretion rate, the minimum response in sodium excretion was observed within thirty minutes following drug administration with a dose of 0.5 mg./kg. This returned to control levels within 2 hours after drug administration. However, after a dose of 1 mg./kg., the natriuretic response persisted throughout the 4 hours of observation. There was a progressively increasing response when the dose was increased to 10 mg./kg.

TABLE 3.—SODIUM EXCRETION FOLLOWING THE ADMINISTRATION OF DICHLORPHENAMIDE AS A SINGLE ORAL DOSE

	C*	D†	I‡
		50 mg.	
	47	58	11
	48	58	10
	53	83	30
	53	78	25
	48	75	27
	46	70	24
	49	87	38
	49	10	−39
	45	53	8
	51	70	19
Average	49	64	15
		100 mg.	
	41	74	33
	45	63	18
	45	130	85
	53	120	67
	51	125	74
	50	106	56
	50	154	104
	48	122	74
	42	126	84
	54	74	20
Average	48	109	61

*C—Control, sodium excretion, mEq./24 hours
†D—Drug, sodium excretion, mEq./24 hours
‡I —Increase in sodium excretion, mEq./24 hours

There was an increase in potassium excretion at all dosage levels which paralleled the sodium excretion rate. However, this effect on potassium excretion was not as marked as was the a.m. and 6 p.m.) showed a slight increase in sodium, potassium, and bicarbonate and, to a lesser degree, in chloride excretion. Urinary pH remained elevated throughout the 24-hour period.

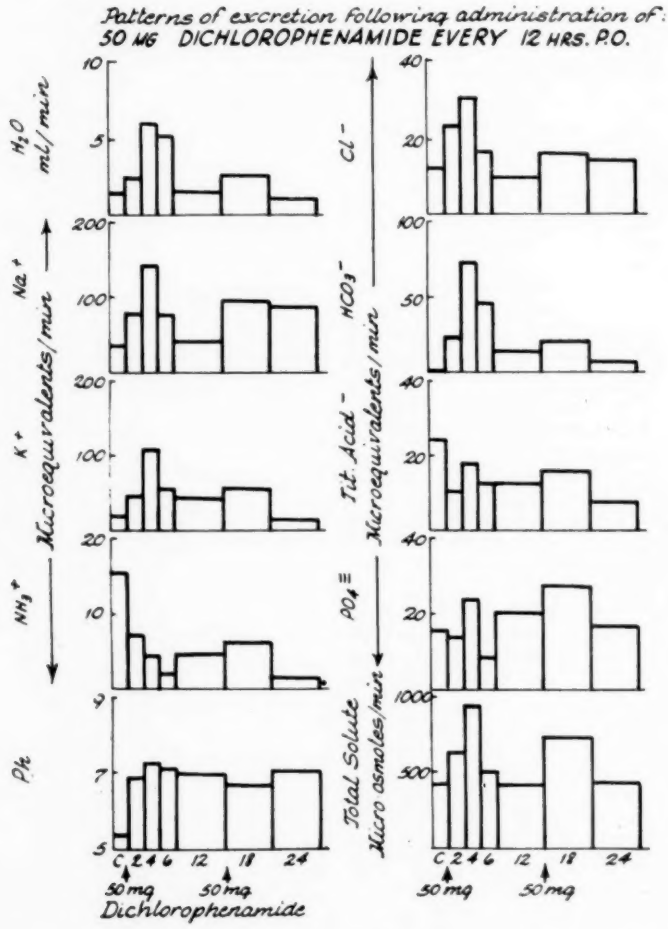

Fig. 1.—Electrolyte excretion pattern following administration of 50 mg. dichlorphenamide twice daily. There is a moderate increase in sodium, potassium and bicarbonate excretion.

natriuretic effect of the dichlorphenamide.

B. RESULTS OF CLINICAL BIOASSAY. The electrolyte excretion pattern (Fig. 1) following oral administration of 50 mg. of dichlorphenamide twice daily (6

The electrolyte excretion pattern following 500 mg. as a single oral dose showed changes lasting only for the first 6 hours (Fig. 2). Sodium excretion was approximately the same as with the lower dose, but this effect per-

sisted for only 6 hours. Potassium and bicarbonate excretion rates were less than those observed with the lower dose while there was a transitory but marked increase in chloride excretion.

dium (about 45 mEq.). The average increase in the 24-hour urinary sodium was 15 mEq. after the 50 mg. dose and 61 mEq. after the 100 mg. dose (Table 3). No toxicity was encountered

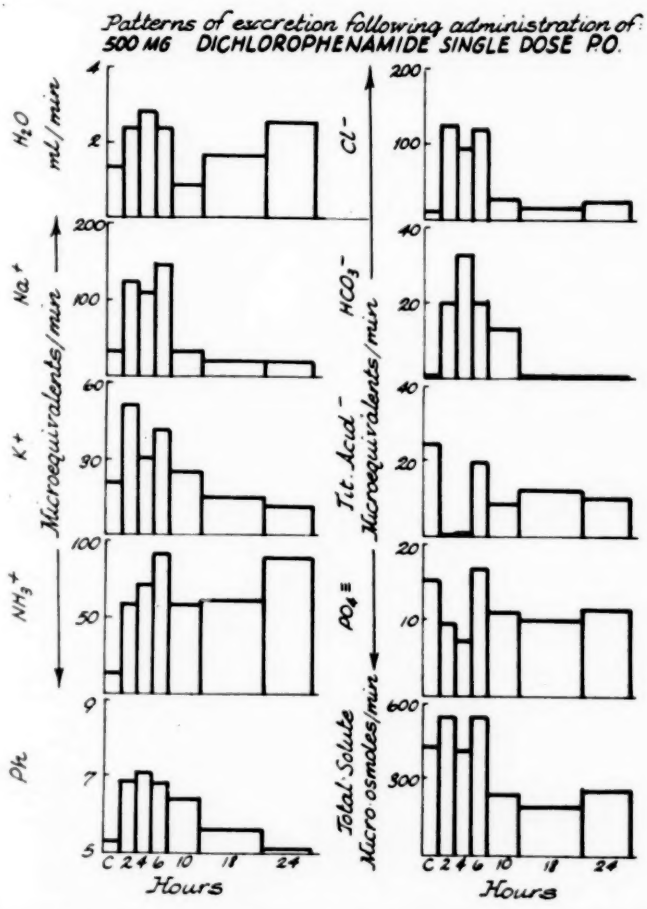

Fig. 2.—Electrolyte excretion pattern following administration of 500 mg. dichlorphenamide as a single oral dose. Increases in sodium, potassium and bicarbonate excretion are approximately equal to those seen with the lower dose, but are of transitory (6 hours') duration.

Urinary pH remained elevated for only the first 6 hours.

Since the patients were balanced on a diet containing 50 mEq. of sodium, the control excretion in the urine was approximately 90% of the dietary so-

in the assay at these dose levels. When these increases are compared to the increases following the administration of a standard parenteral mercurial diuretic agent (meralluride), the dosage response curves were found to be

highly significant and parallel so that a potency estimation could be made (Ford, Spurr and Moyer[2]). With meralluride as "one," dichlorphenamide was 0.5, that is, 0.5 times as potent as meralluride, or 100 mg. of orally administered dichlorphenamide produced an increase in sodium excretion equivalent to 40 mg. Hg (1 ml.) meralluride (Mercuhydrin) (Fig. 3).

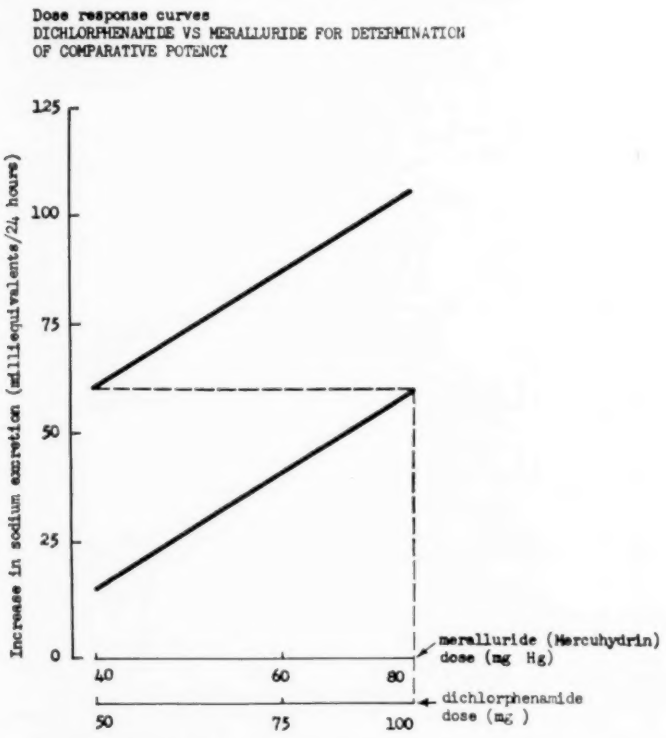

Fig. 3.—Potency estimation of dichlorphenamide. This agent is 0.5 times as potent as the standard, meralluride (meralluride equals 1.0).

In the 2 patients who received 50 mg. twice daily for 5 consecutive days, there was a continuing excretion of sodium and bicarbonate and, to a lesser degree, of potassium and chloride until the body stores were depleted. The only significant electrolyte alteration associated with this response was a slight rise of blood urea nitrogen. However, this was associated with a concomitant rise in hematocrit so it was felt that these changes were due to dehydration rather than impairment of renal function (Fig. 4). There was a tendency towards CO_2 depression, but this was slight and not clinically significant.

Discussion. In pre-clinical investigation (Beyer[1]), dichlorphenamide was shown to act as a carbonic anhydrase inhibitor. However, unlike acetazolamide (Diamox), this compound caused a definite increase in chloride excretion. Partially as a result of the greater excretion of chloride, this compound does not produce as marked a

metabolic acidosis as that which attends the administration of acetazolamide at equivalent dosage. This difference probably accounts for the fact that the compound retains activity in dogs on chronic administration.

The dosage-response curve relating increasing doses of dichlorphenamide to sodium excretion indicates that the effective clinical dose is between 50 and 100 mg. (as a single dose). Doses in excess of 200 mg. produce progressive gastrointestinal (anorexia, nausea and vomiting) and central nervous system (dizziness, ataxia, tremor, and tinnitus) toxicity symptoms. The potency estimation of dichlorphenamide was determined to be 0.5. Thus,

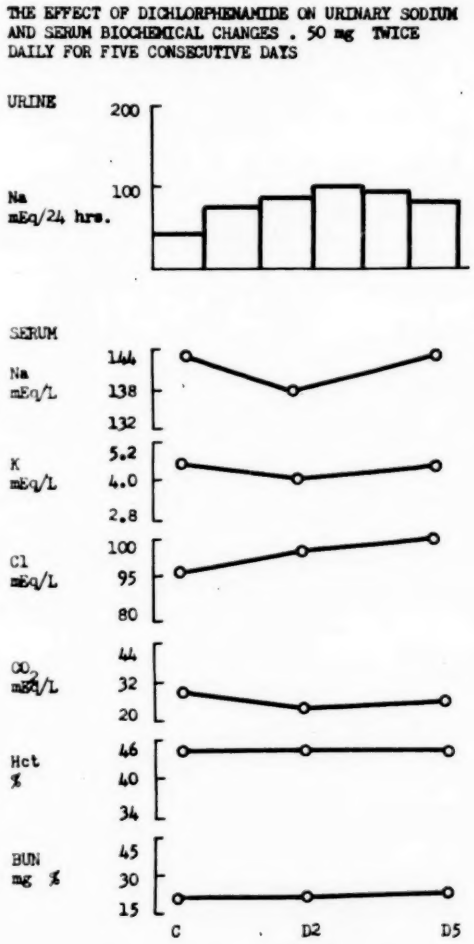

Fig. 4.—Urine and serum electrolytes associated with 5-day administration of dichlorphenamide in a dose of 50 mg. twice daily. The agent continues to be effective until body electrolyte stores are depleted. There is a tendency towards slight CO_2 depression.

100 mg. of orally administered dichlorphenamide produces an increase in sodium excretion comparable to one milliliter of meralluride administered intramuscularly. The potency estimation of dichlorphenamide is approximately twice that of acetazolamide at its maximal effective dose.

Because of the associated chloruresis, dichlorphenamide more closely resembles chlorothiazide in its electrolyte excretion pattern. This similarity is much more apparent at the higher dose (500 mg.). The chloruresis attendant to dichlorphenamide administration is at least partially responsible for the absence of development of systemic acidosis and thus allows this agent to be effective on repetitive administration.

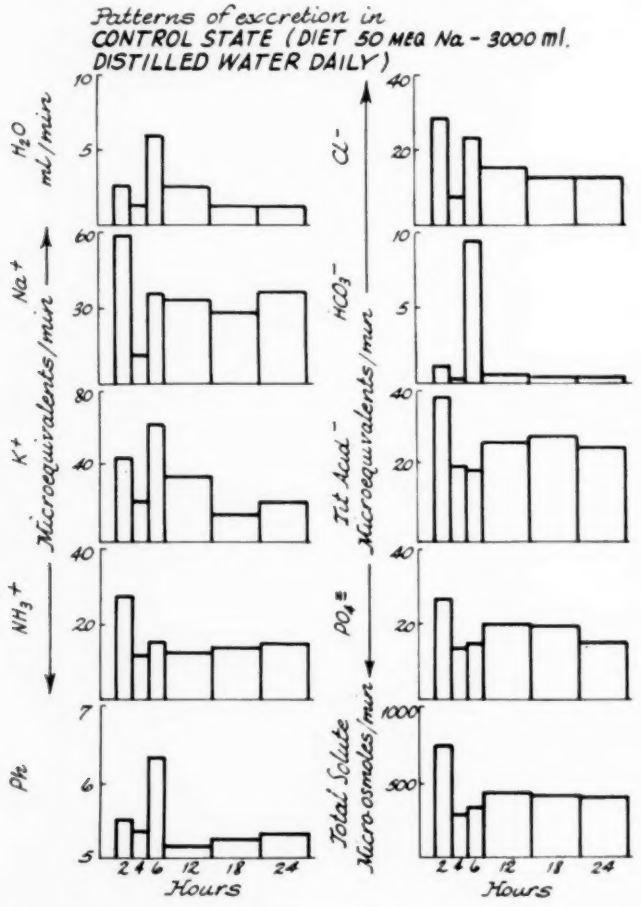

Figure 5.—Electrolyte excretion pattern in the control state.

It is of interest to compare the electrolyte excretion pattern of dichlorphenamide to other diuretic agents, namely meralluride, chlorothiazide, and acetazolamide (Figs. 5, 6, 7, and 8). These data indicate that dichlor-

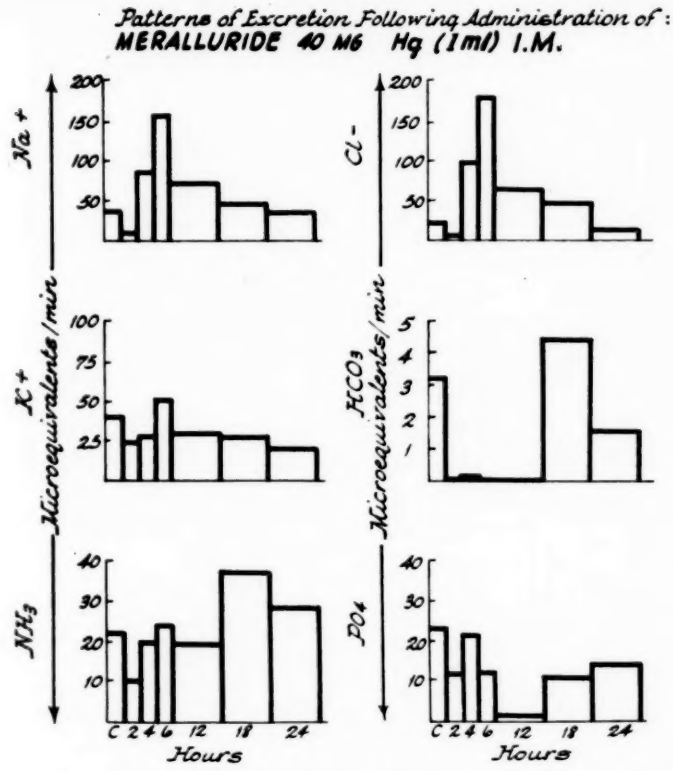

Fig. 6.—Electrolyte excretion pattern following intramuscular administration of meralluride.

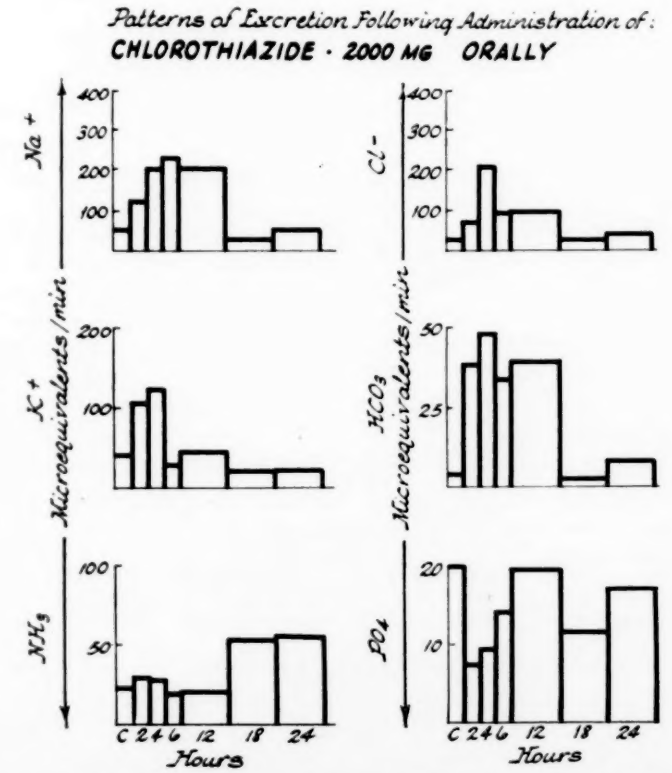

Fig. 7.—Electrolyte excretion pattern following oral administration of chlorothiazide.

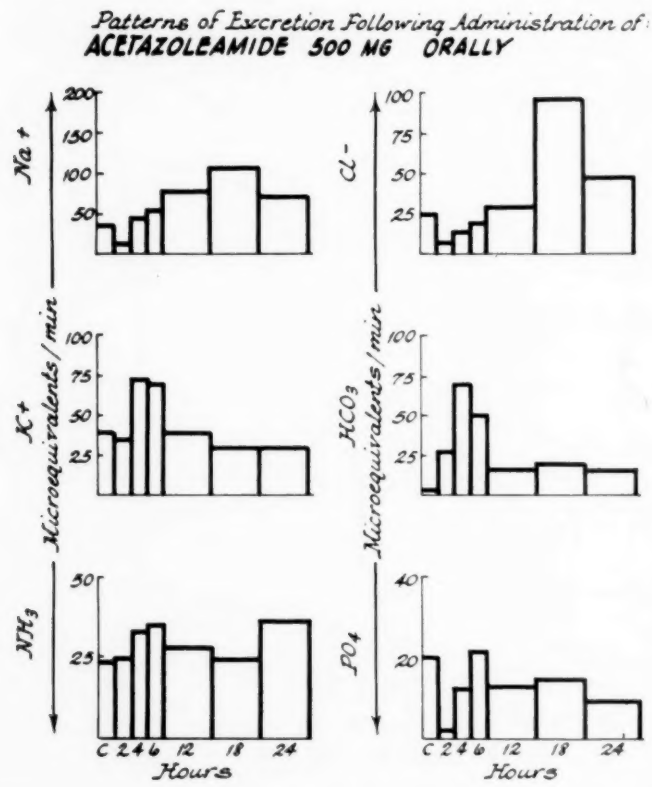

Fig. 8.—Electrolyte excretion pattern following oral administration of acetazolamide.

phenamide is a useful oral diuretic agent, but it is only moderately potent and indicated in the treatment of patients with mild heart failure or for prolonging the period between injections of the organomercurials in patients with moderately severe to severe heart failure. This agent is continually effective on chronic administration and does not show the propensity to develop systemic acidosis that is seen with other carbonic anhydrase inhibitors.

Conclusions. 1. Dichlorphenamide is an effective oral diuretic of moderate potency. At optimum clinical dosage, there are no significant side effects.

2. Because of associated chloruresis, this agent does not produce acidosis as readily as other carbonic anhydrase inhibitors and, therefore, retains its effectiveness with chronic administration.

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(Interlingua on page 182)

THE RECTAL ABSORPTION OF MERCAPTOMERIN TAGGED WITH Hg^{203}*

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The search continues for a simple method of administering a mercurial diuretic agent. When a single suppository of mercaptomerin sodium (Thiomerin) labeled with Hg^{203} was given to human subjects, absorption was poor and diuresis rarely followed (Aikawa and Carlson[1]). The parenteral administration of two doses of this material to rabbits, however, resulted in an accumulation of radioactivity in the kidney (Aikawa, Blumberg and Catterson[2]). This finding suggested the possibility that, in human subjects, the administration of suppositories on successive days might result in a renal cumulative effect of sufficient magnitude to induce diuresis.

In the present study 10 patients in congestive heart failure were given, on 3 successive days, a single suppository of mercaptomerin sodium tagged with Hg^{203}. The volume and radioactivity of the urine were measured in all patients; the radioactivity of the serum was determined in 4 subjects.

Material and Methods. Suppositories† were made up in a cocoa butter base to contain 0.5 gm. of mercaptomerin sodium (equivalent to 165 mg. of mercury) and 500 microcuries of radioactivity as Hg^{203}. The subjects selected for study were 10 hospitalized patients, all of whom were being treated intensively for congestive heart failure and all of whom had demonstrable pitting edema. None of the subjects had evidence of any gastrointestinal abnormality. All patients were at bed rest and were on a low-salt hospital diet. Fluids were given without restriction.

Before breakfast on 3 consecutive days a suppository was inserted deep into the rectum with the gloved index finger, and the subject was requested to retain the suppository as long as possible. Specimens of blood and urine were obtained at the intervals specified in Table 2.

ASSAY OF RADIOACTIVITY. Samples of serum and urine were placed, without prior treatment in Pyrex test tubes, which were stoppered and were then placed individually in a Nuclear Model DS–3 scintillation well counter for gamma ray assay. In order to obviate loss of mercury through volatilization, these samples were never subject to temperatures higher than 75° F.

Results. The values for the daily urinary excretion of radioactivity fol-

*This study was supported in part by grants-in-aid from the American Heart Association, the Colorado Heart Association, and Wyeth Laboratories, and in part by a contract with the U.S. Atomic Energy Commission.

Hg^{203} was obtained from the Oak Ridge National Laboratory, Oak Ridge, Tennessee, on allocation from the U.S. Atomic Energy Commission.

†Mercaptomerin sodium suppositories labeled with Hg^{203} were synthesized by the Wyeth Institute for Medical Research.

TABLE 1.—THE RECTAL ABSORPTION OF MERCAPTOMERIN LABELED WITH Hg^{203}

The Urinary Excretion of Radioactivity Following the Rectal Administration, on Three Successive Days, of Thiomerin Suppositories Tagged with Hg^{203}

	0–24 Hrs.			*24–48 Hrs.*			*48–72 Hrs.*			*72–96 Hrs.*			*96–120 Hrs.*		
Patient	% Hg*	*Hg (mg.)*	*Vol. (ml.)*	% Hg*	*Hg (mg.)*	*Vol. (ml.)*	% Hg*	*Hg (mg.)*	*Vol. (ml.)*	% Hg*	*Hg (mg.)*	*Vol. (ml.)*	% Hg*	*Hg (mg.)*	*Vol. (ml.)*
1	1.74	2.87	1,265	2.50	4.13	1,060	1.51	2.49	820						
2	1.20	1.98	2,080	0.90	1.49	1,320	0.84	1.39	1,420			1,450			
3	0.16	0.26	575	0.44	0.73	360	0.63	1.04	580						
4	1.37	2.26	850	1.07	1.77	1,240	0.64	1.06	540						
5	1.19	1.96	410	0.47	0.78	600	0.38	0.63	380						
6	2.19	3.60	3,400	0.47	0.80	4,090	2.02	3.30	5,040	0.03	0.05	3,900	0	0	4,000
7	2.16	3.60	2,960	0.12	0.20	3,060	0.53	0.90	2,775	0.21	0.30	3,575	0.29	0.50	3,000
8	0.72	1.20	815	0.71	1.20	800	1.02	1.70	1,270	0.09	0.10	865	0	0	440
9	0.15	0.20	880	1.04	1.70	1,270	0.86	1.40	1,120	0.32	0.50	770	0.08	0.10	1,210
10	1.01	1.67	1,900	2.42	3.99	980	0.97	1.60	875	0.19	0.31	260	0.14	0.23	1,140

Legends: % Hg* = per cent radioactivity in 24-hour urine
Hg = milligrams of mercury excreted in 24-hour urine
Vol. = volume of 24-hour urine

TABLE 2.—SERUM MERCURY CONCENTRATIONS AT VARIOUS TIME INTERVALS FOLLOWING THE ADMINISTRATION OF THIOMERIN SUPPOSITORIES TAGGED WITH Hg^{203}

	0–24 Hours		*24–48 Hours*		*48–72 Hours*	
Patient	*Time After Administration of Suppository (Hours)*	*Serum Level (μg/ml.)*	*Time After Administration of Suppository (Hours)*	*Serum Level (μg/ml.)*	*Time After Administration of Suppository (Hours)*	*Serum Level (μg/ml.)*
1			3	0.23	3	0.20
			6	0.14		
			9	0.12	9	0.05
	24	0.02	24	0.02	24	0.01
3	3	0.03	3	0.04	3	0.16
	6	0	6	0.13	7	0.18
	7	0.03	11	0.10		
4	3	0.26	3	0.21	3	0.23
	6	0.20	6	0.17	7	0.20
	10	0.13	11	0.11		
5	3	0.32	3	0.17	3	0.28
	6	0.19	6	0.11	7	0.14
	10	0.15	11	0.06		

lowing rectal administration of each suppository were low; in no case did the 24-hour specimen of urine contain more than 2.50% of the suppository dose, the values ranging downward to 0.15%. No definite increase in urine volume occurred during or after the administration of the three mercaptomerin suppositories, nor was there any obvious correlation between the urinary excretion of radioactivity and the daily urine volume.

In most instances the maximum concentration of radioactivity in the serum was attained within 6 hours, the highest values usually being obtained at 3 hours.

In general, there appeared to be a correlation between the total urinary excretion of radioactivity and the maximum serum concentration of Hg^{203}.

Discussion. The results of the present study suggest that the absorption from suppositories containing 165 mg. of mercury as Thiomerin is insufficient to induce diuresis when a single daily suppository is given *per rectum* on 3 successive days. It has been previously calculated that a minimum of 4.5 mg. of mercury must be absorbed from a single suppository before a diuretic response will occur (Aikawa and Carlson[1]). In the present study absorption of this magnitude was never attained during a 24-hour period, nor was there any evidence that a renal cumulative effect sufficient to induce diuresis had occurred. In no instance did the concentration of mercury in the serum reach a level of 0.5 microgram per cubic centimeter, that level which previously was found to be associated with an increase in urine volume (Aikawa and Carlson[1]).

A previous clinical study (Daly[3]) on the use of Thiomerin in suppository form has suggested that rectal administration of this drug is effective in maintaining an adequate diuretic response if repeated doses are used; this observation suggests that, although the proportion of mercury absorbed from each suppository is small, repeated administration does produce a renal cumulative effect. Whether the concentration of mercury in the kidney can be increased by the repeated administration of suppositories at more frequent intervals can be definitely detemined by *in vivo* surface counting over the renal areas following the administration of tagged Thiomerin in this manner; such studies are now in progress. It is our clinical impression from limited observations that, in certain patients, the daily administration of Thiomerin suppositories does indeed decrease the frequency with which it is necessary to give parenteral mercurials, but we know of no way of predicting which ones will respond in this fashion.

In the previous study, the urinary excretion of radioactivity following the rectal administration of Thiomerin was lowest in the subjects with edema (Aikawa and Carlson[1]). In the present study, which was limited to patients with congestive heart failure and clinical edema, the figures for the daily urinary excretion of radioactivity were higher than those previously obtained (Aikawa and Carlson[1]), although not high enough to be associated with diuresis. The higher figures in the present study are attributed to a more careful selection of cooperative patients; all the subjects in this study are known to have retained the suppositories for at least 3 hours, whereas in the initial study the material may have been lost sooner.

Summary. Three suppositories of mercaptomerin sodium labeled with Hg^{203} were administered to 10 subjects with congestive heart failure, one suppository being given *per rectum* on each of 3 successive days. Serial speci-

mens of blood and urine were obtained. It was found that the amount of mercury absorbed from any single suppository was less than 4.5 mg. There was no evidence of a renal cumulative effect sufficient to induce diuresis.

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3. **Daly, J. W.**: Am. J. Med. Sci., **228**, 440, 1954.

SUMMARIO IN INTERLINGUA

Le Absorption Rectal De Mercaptomerina Marcate Con Hg^{203}

Tres suppositorios de natrium de mercaptomerina marcate con Hg^{203} esseva administrate a 10 subjectos con congestive disfallimento cardiac, un suppositorio per die in tres dies successive per via rectal. Specimens serial de sanguine e de urina esseva obtenite. Esseva trovate que le quantitate de mercurio absorbite ab omne suppositorio individual esseva minus que 4,5 mg. Nulle signo esseva notate de un effecto renal cumulative de magnitudes sufficiente pro inducer diuresis.

SUMMARIO IN INTERLINGUA

(See page 168 for original article)

Dichlorphenamido Como Agente Diuretic

1. Dichlorphenamido es un efficace diuretico oral de potentia moderate. Al optimo del dosage clinic, il ha nulle significative effectos lateral.

2. A causa del associate chlorurese, iste agente non produce acidose tanto facilemente como altere inhibitores de anhydrase carbonic, e per consequente illo retine su efficacia mesmo in administration chronic.

SUMMARIO IN INTERLINGUA

(See page 183 for original article)

Comparation De Penicillina G e Penicillina V in Le Tractamento De Streptococcal Dolor De Gurgite

Le curso del morbo, le processo del eradication del streptococcos ab le gurgite, e le production de antistreptolysina-O esseva simile in duo gruppos de recrutas del Fortias Aeree suffrente de dolor de gurgite, tractate con penicillina G in le prime gruppo e con penicillina V in le secunde. Le situation del test esseva que 43 patientes recipeva 250.000 unitates de penicillina G per via oral tres vices per die durante 10 dies e 43 alteres recipeva 200.000 unitates de penicillina V etiam per via oral e etiam tres vices per die durante 10 dies.

Le conclusion es que in le dosages usate, penicillina V non esseva superior a penicillina G.

A COMPARISON OF PENICILLIN G AND PENICILLIN V IN TREATMENT OF STREPTOCOCCAL SORE THROAT*

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and

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Penicillin is the drug of choice for treatment of streptococcal sore throat[3]. The present recommendation of the American Heart Association for oral penicillin is 200,000 to 250,000 units 3 times a day for a full 10 days. Lower doses and shorter duration of therapy do not eradicate the infecting organism consistently and therefore may not prevent the occurrence of rheumatic fever or glomerulonephritis.

In recent years a new form of penicillin, phenoxymethyl penicillin (penicillin V), has been described and shown to be effective *in vitro* against the group A streptococcus (Martin, Nichols, and Heilman[7], White *et al.*[12]). Several investigators have reported small series of patients with streptococcal infections that responded satisfactorily to the administration of penicillin V (Cronk and Navmann[4], Martin, Nichols, and Heilman[8], Wehrle, Feldman, and Kuroda[10]). Breese and Disney[1], using penicillin V for treatment of 110 children with streptococcal infections that included pyogenic infections and the carrier state, as well as streptococcal sore throat, reported an over-all "cure" of approximately 90%. In addition, Wehrle *et al.*[11] described the response of patients with scarlet fever to oral penicillin V and favorably compared their results to reported results with oral and parenteral administration of penicillin G. Blood level assays, following oral doses of penicillin V comparable in weight to penicillin G, have shown that levels 2 to 7 times higher were attained with the former (Martin, Nichols, and Heilman[7], Rinsler and Cunliffe[9]). The increased resistance of penicillin V to destruction by acid makes it more dependable in its absorption than penicillin G when given with meals (Jones and Finland[6]).

It seemed desirable to determine in a controlled study whether or not these apparent advantages of pencillin V would make it a more useful drug than penicillin G in the treatment of streptococcal sore throat. This study describes comparative effects of penicillins V and G on the clinical course, streptococcal

*This investigation was conducted under the sponsorship of the Commission on Acute Respiratory Diseases, Armed Forces Epidemiological Board, and was supported by the Offices of the Surgeons General, Departments of the Army and Air Force, Washington, D.C.

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carrier state, and antibody response of young Air Force recruits with acute streptococcal sore throat.

Methods. Throat swabs, obtained from all patients admitted to the base hospital with respiratory illness, were planted directly on 5% sheep's blood agar culture plates. Patients whose cultures showed 11 or more colonies of beta-hemolytic streptococci were included in the study initially, but were subsequently excluded if the streptococci were found not to be Lancefield Group A.

Alternate patients received buffered potassium penicillin G, 250,000 units three times daily, or phenoxymethyl pencillin (V), 200,000 units three times daily.* These doses were used because of their proprietary availability. Medication was given with or within one hour after each meal. The drugs were administered by a technician of the laboratory, and physicians participating in the study had no knowledge of the type of penicillin received by the patients. While in the hospital patients received no other drugs. Treatment was administered for 10 days, 5 at the hospital and 5 on an outpatient basis. Careful records were kept to insure that each patient received his full course of treatment. Those receiving incomplete treatment were excluded from the study.

TABLE 1.—COMPARABILITY OF PATIENTS AT THE START OF TREATMENT OF STREPTOCOCCAL SORE THROAT WITH PENICILLIN G OR PENICILLIN V

	Treatment			
	Penicillin G (47 pts.)		*Penicillin V (43 pts.)*	
	No.	*%*	*No.*	*%*
Time between onset of illness and treatment.				
36 hours or less	13	28	11	26
60 hours or less	32	68	30	70
72 hours or less	39	83	35	81
History of tonsillectomy	15	32	14	33
Initial Throat Culture				
More than 50 colonies of beta hemolytic streptococci.	32	68	29	69
Group A	47	100	43	100
Type 6	5	11	8	19
18	19	40	8	19
19	18	38	23	54
Other	5	11	4	8
Antistreptolysin-O less than 100 units	29	67	25	61
White blood count				
less than 11,000	10	21	9	21
11,000 and greater	32	68	31	72
unknown	5	11	3	7

The following laboratory and clinical observations were made: Cultures from the nose and throat were obtained daily during the hospital stay and then on the 10th, 12th, 15th, 17th, and 21st days after starting treatment. Acute and convalescent blood specimens were obtained for the determination of antistreptolysin-O titers. Beta-hemolytic streptococci were grouped and typed by the Lancefield method. Each patient was examined daily while in the hospital and his symptoms were recorded by 12-hour intervals from the start of treatment.

*Both forms of penicillin were supplied by Edward Roberts, M.D., Wyeth Laboratories, Inc., Philadelphia, Pa.

Before starting the study, both physicians spent considerable time seeing patients with streptococcal disease and established complete agreement in the grading of physical signs.

Results. Ninety patients met the criteria of group A streptococci on admission culture and a complete course of treatment. Forty-seven were treated with penicillin G and 43 received penicillin V. A comparison of the two groups of patients at the start of therapy is shown in Table 1. It is seen that the duration of illness, history of tonsillectomy, degree of positivity of throat cultures, antistreptolysin-O titers, and white blood counts were similar. There was a difference, however, in the distribution of the streptococcal types. Type 19 occurred less often and type 18 more often in patients treated with penicillin G. The average age was 18 years for both groups with a range for the penicillin G group of 17 to 27 years and for the penicillin V group of 17 to 22 years.

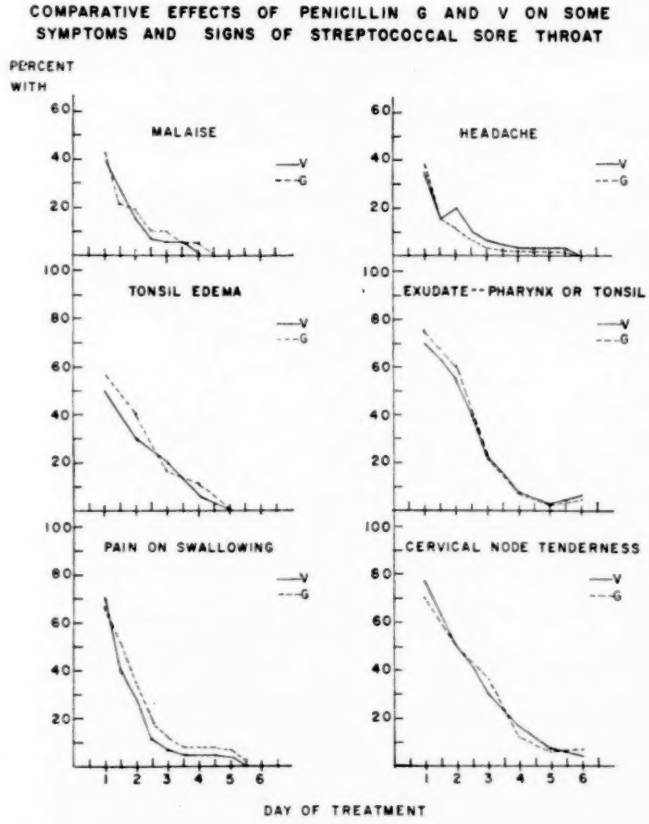

Fig. 1

At the onset of treatment, symptoms and signs were also similar in both groups. Figure 1 shows the percentage of patients with certain symptoms and signs of streptococcal sore throat at the start of treatment and during the period of hospital observation. There

was no apparent difference between the two groups, either in the findings presented in Fig. 1 or in other symptoms and signs such as feverishness and tonsillar or pharyngeal injection and edema. No patient in either group remained in the hospital after the fifth day of treatment because of continued illness or a bacterial complication.

tients in the penicillin V treated group and 15% of those in the penicillin G group still had positive throat cultures at this time. After the second day of treatment, positive cultures were present in only 2% of the cases in each group.

The results of the throat cultures obtained during and after treatment from

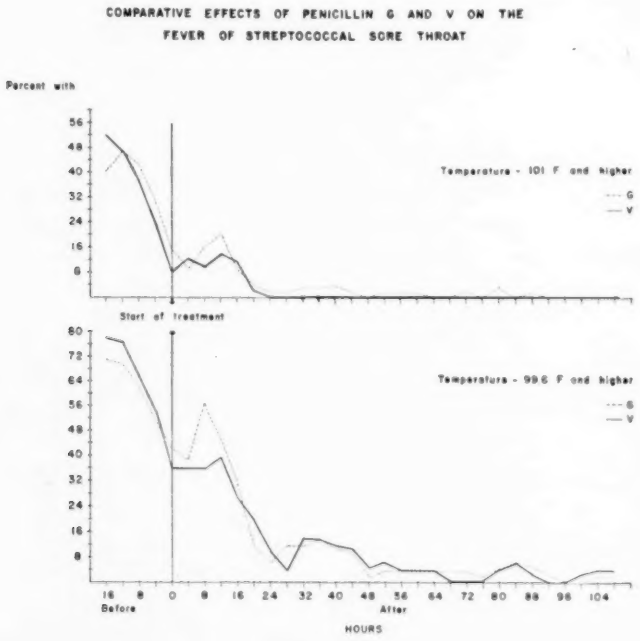
COMPARATIVE EFFECTS OF PENICILLIN G AND V ON THE
FEVER OF STREPTOCOCCAL SORE THROAT
Percent with
Temperature - 101 F and higher
G
V
Start of treatment
Temperature - 99.6 F and higher
G
V
16 8 Before 0 8 16 24 32 40 48 56 64 72 80 88 96 104 After
HOURS

Fig. 2

The effects of the two forms of therapy on fever are shown in Fig. 2. Except for a slight increase in the penicillin G group 8 hours after the start of treatment, the course of fever in the two groups both before and after therapy was similar. Since treatment began at 8 a.m., the slight upswings in the curves at 8 and 32 hours represent afternoon temperatures.

There was a sharp drop in positive cultures one day after the start of treatment. Nine per cent of the patients in the penicillin V group and 11% in the penicillin G group had positive cultures at this time. Two days after the start of treatment, positive cultures were present in only 2% of the cases in each group.

The results of the throat cultures obtained during and after treatment from those patients with persistence or reappearance of their infecting type are shown in Table 2. Twenty-eight patients from the penicillin G group and 27 patients from the penicillin V group were available for culturing for the entire 21 days. Those patients from whom the infecting type was isolated 7 or 11 days after the end of treatment thus represented approximate 14 and 11% bacteriological relapse rates in the penicillin G and V groups, respectively. Of course, reacquisition of the same

type cannot be excluded. Case A–22, who had persistently positive nose cultures as well as throat cultures, had an antral sinusitis that required surgical drainage. No reason for persistence of positive cultures was found in case B–30. In no instance was the reappearance of a positive culture associated with symptoms.

Convalescent sera were obtained 14 to 28 days after the onset of illness from 40 and 36 patients in the penicillin G and V group, respectively. Antistreptolysin-O rises of two tubes or more occurred in 27.5% of the cases in the penicillin G group and in 33.3% of the cases in the penicillin V group.

TABLE 2.—PERSISTENCE OR REAPPEARANCE OF INFECTING TYPE OF STREPTOCOCCUS AFTER TREATMENT WITH PENICILLIN G OR V

			Throat Culture°—Day of Treatment										
Treatment	*Case*	*Streptococcal Type*	*0*	*1*	*2*	*3*	*4*	*5*	*6*	*10*	*12*	*15*	*17*	*21*
G	A–13	6	2	0	0	0	0	0	0	0	0	0	1	3
	A–22	18	3	3	3	2	3	0	1	3	3	0	4	–
	A–32	18	3	3	0	0	0	0	0	0	–	0	0	3
	A–33	19	2	3	0	0	0	0	–	0	0	0	0	4
V	B–18	19	4	3	0	0	0	0	0	0	0	0	2	2
	B–26	18	3	3	0	0	0	0	0	0	0	0	4	–
	B–30	19	3	4	0	2	0	0	2	0	0	4	1	0

°0 = No beta-hemolytic streptococci.
1 = 1 to 10 colonies on blood agar plate.
2 = 11 to 49 " " " " "
3 = 50 plus " " " " "
4 = Almost pure culture of beta-hemolytic streptococci.
– = Culture lost or not obtained.

Discussion. The course of illness, eradication of streptococci from the nose and throat, and development of streptococcal antibody as determined by the antistreptolysin-O titer were similar in two groups of patients with acute streptococcal pharyngitis treated orally with either buffered potassium penicillin G or phenoxymethyl penicillin (penicillin V) for 10 days. The dose of penicillin G was larger (250,000 units, t.i.d.) than that of penicillin V (200,000 units, t.i.d.) so that strict comparability of the two penicillin forms by weight is not possible. The tablet sizes used, however, are those readily available to most physicians and are the sizes most likely to be used in treatment of streptococcal sore throat. In addition, the dose and duration of treatment using penicillin G are those presently recommended for the treatment of streptococcal tonsillitis and pharyngitis to prevent the nonsuppurative complications, rheumatic fever and acute glomerulonephritis, which did not occur in this small series of patients. With the degree of streptococcal eradication and suppression of antistreptolysin-O equal in the two groups we would expect similar equality in the prevention of rheumatic fever and nephritis (Catanzaro *et al.*[2], Houser *et al.*[5]).

Although penicillin blood levels were not done in this study, ample evidence has accumulated that penicillin V will result in higher and more sustained levels than equal amounts of penicillin G. That this is no advantage in the treatment of streptococcal

sore throat at the dosage level used in this study has been demonstrated. It is possible that smaller doses of penicillin V might have been as effective as those used, but with the prevention of nonsuppurative sequelae of streptococcal sore throat as the object of treatment, it is unlikely that one would be willing to reduce the dose below that used in this study. Indeed, the percentage of patients with reappearance of their infecting serologic type of streptococcus after cessation of treatment suggests that an increased dose might have been indicated. Since the patients in this study remained in an environment where streptococcal disease was epidemic, such reappearance may have been the result of reinfection rather than bacteriologic relapse. Evidence from other studies, however, shows that in most instances this reappearance is the result of relapse (Catanzaro *et al.*[2], Houser *et al.*[5]).

Since no attempt was made to have the patients take their penicillin at least ½ hour before or more than 2 hours after meals, it was usually taken with the meal or immediately after. Thus, no practical advantage for penicillin V in its increased resistance to destruction by stomach acid was apparent.

Summary. The course of illness, eradication of streptococci from the throat, and production of antistreptolysin-O were similar in two groups of Air Force recruits with group A streptococcal sore throat treated with either penicillin G or penicillin V. Forty-seven patients received 250,000 units of penicillin G by mouth three times a day for 10 days and 43 patients received 200,000 units of penicillin V by the same schedule.

It is concluded that, in the dosages used, penicillin V was not superior to penicillin G.

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(Interlingua on page 182)

CHANGES IN BODY WATER COMPARTMENTS DURING THE COURSE OF ACUTE RENAL INSUFFICIENCY AND THEIR RELATION TO WATER AND ELECTROLYTE EXCRETION*

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Acute renal insufficiency is a clinical syndrome characterized by rapid progressive uremia and includes a wide variety of disorders among which is acute renal failure. The experimental analogue of this syndrome is the bilaterally nephrectomized animal and the occurrence of a relative or absolute increase in total body water during the course of acute renal insufficiency through the mechanism of catabolism of tissue with production of water of oxidation and release of preformed water, has been adequately documented in dogs (Hamburger and Mathe[8]), rabbits (Nairn[11]), and sheep (McDonald, Coats and Munro[10]). In man a limited number of single studies of body water compartments during the course of acute renal failure have indicated an increase in total body water and in extracellular fluid volume (Schwartz, Tomsovic and Schwartz[13], Sirota and Kroop[15], and Smith, Madisso and Pitts[17]). These studies, coupled with extensive clinical observations, have led Swan and Merrill[19] to state that the polyuria of the diuretic phase of acute renal failure does not entirely represent an inability of the kidneys to conserve electrolytes and water, but is the mechanism for the excretion of excessive amounts of electrolytes and water that have accumulated during the course of the disease.

The purpose of this study was to accumulate additional information about the changes in body fluids that occur during the course of acute renal insufficiency and to test the hypothesis of Merrill concerning the diuretic phase of acute renal failure.

Experimental Material and Methods. Eight patients with acute renal insufficiency were studied. Brief clinical summaries of each case are presented in Table 1. Several of the pa-

*Part of this data was presented at the Annual Meeting of the Midwestern Section of the American Federation for Clinical Research, on November 8, 1956, in Chicago, Illinois.

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Some of the material used in this investigation was generously suppled by the following individuals: Antipyrine, Dr. B. L. Martz, Eli Lilly & Co.; Acetazolamide, Dr. C. H. Demos, Lederle Laboratories Division of American Cyanamid Co.; Pitressin and Tetra-Ethyl-Ammonium Chloride, Dr. F. M. Wessels, Parke Davis & Co.

tients, who were transferred from other hospitals to the University of Illinois Research and Educational Hospitals with a diagnosis of acute renal failure, were found after observation in this institution to be suffering from other conditions producing acute renal insufficiency. Prior to our studies the patients were usually managed by the application of the formula: fluid intake per 24-hour period equals output plus one liter. In our institution, fluid intake (as dextrose in water) was limited to provide for a daily weight loss of ¼ kilogram in the oliguric phase, and to a maximum intake of 3 liters per 24-hour period during the diuretic phase. Antipyrine space was used as a measure of total body water. Analysis of antipyrine was done by the following modifications of the method of Brodie *et al.*[4]: (1) After addition of the zinc sulfate and sodium hydroxide solutions to the plasma, the mixture was allowed to stand until the precipitate began to settle before centrifuging, (2) 2.0 ml. of the filtrate was used for the analysis for antipyrine, (3) 0.06 ml. of 4 N sulfuric acid was added to the filtrate instead of one drop, (4) 0.1 ml. of sodium nitrite was used instead of two drops and (5) the maximal optical density was obtained by continuous reading of the optical density (this usually occurred 10 to 15 minutes after addition of the sodium nitrite). Duplicate analyses were made in all instances.

TABLE 1.—CLINICAL DATA

Pt.	*Age*	*Sex*	*Clinical Diagnosis*	*Duration of Oliguria°*	*Duration of Diuresis°°*	*Pathological Diagnosis (Kidney)*
H.F.	23	M	? Acute Glomerulonephritis	10 days anuria	—	Death Subacute glomerulonephritis
E.T.	43	F	Acute renal failure Postoperative shock	12 days	3 days	Death No necropsy
N.T.	51	F	Diabetic nephropathy ? Hypersensitivity angiitis Secondary to sulfonamides	6 days	—	Death Arteriolo-nephrosclerosis Pyelonephritis
V.A.	46	F	Acute renal failure Hypotension following blood transfusion	9 days	14 days	Recovered
M.S.	25	F	Acute renal failure Etiology undetermined	4 days	7 days	Recovered
M.Z.	45	F	Acute renal failure Shock following massive gastrointestinal hemorrhage	15 days	—	Death Acute tubular necrosis
J.S.	70	M	Acute renal failure Secondary to aortogram	—	—	Death Multiple small renal infarcts
L.G.	32	F	Acute renal failure Hypotension following incompatible blood transfusion	6 days	11 days	Recovered

°24-hour urine output less than 400 ml.
°°From the end of the oliguric phase until body weight stabilized.

The radio sulfate° space was used as a measure of extracellular fluid volume employing the method of Ryan and his coworkers[12]. The constant infusion technique was used for measurement of renal dynamics. Clearances of inulin (C_{In}) and para-

°Obtained from Abbott Laboratories, North Chicago, Illinois, on allocation from the Atomic Energy Commission.

aminohippurate (C_{PAH}) were used as measures of glomerular filtration rate and renal plasma flow respectively. Timed urine collections were made through an indwelling bladder catheter with distilled water and air washout. Mid period blood sampling was done through an indwelling needle in an appropriate vein. Ten-minute periods were employed. Three control periods were obtained at the beginning of each experiment. Acetazolamide was administered as a priming dose of 10 mg./kg., followed by sustaining doses of 20 mg./kg. administered at a minimum rate of 10 mg./min. The dose of pitressin was 0.30 to 0.57 milliunits/kg. administered in a single injection. Inulin concentration in plasma and urine was determined by the method of Kendrick[9]; PAH concentration in plasma and urine, by the method of Smith, Finklestein, Aliminosa, Crawford, and Graber[16]; and sodium and potassium concentrations were measured with a flame photometer.

TABLE 2.—BODY WATER COMPARTMENTS DURING THE COURSE OF ACUTE RENAL FAILURE

Pt.	Day After Onset	Weight Kg.	Antipyrine Space		Radiosulfate Space		Antipyrine Space minus Radiosulfate Space	
			Liters	% Body Weight	Liters	% Body Weight	Liters	% Body Weight
H.F.	11*	55.3	38.5	69.7	19.8	35.8	18.7	33.8
E.T.	6	56.2	26.1	46.5	12.8	22.6	13.3	23.7
L.G.	6	63	45.9	72.9	13.9	22.1	32.0	50.8
	146	59.6	28.4	47.6	11.3	20.0	17.1	28.7
	187	62.1	32.0	51.6	10.8	17.4	21.2	34.1
V.A.	5	54.6	34.5	60.7	15.0	27.5	19.5	35.7
	19	42.7	18.0	42.2	7.5	17.6	10.5	24.6
	54	44.9	18.4	41.0	8.0	17.8	10.4	23.2
M.S.	3*	40.2	29.1	72.4	13.4	33.3	15.7	39.1
	23*	38.2	23.1	60.4	9.0	23.6	14.1	36.9
	59*	44.6	25.3	56.7	10.4	23.3	14.9	33.4
	172*	48.1	21.5	44.7	8.7	18.1	12.8	26.6
M.Z.	5	68.9	31.7	46.1	15.5	22.5	16.2	23.5
	7	68.7	32.6	47.4	—	—	—	—
	10	67.8	30.7	45.3	—	—	—	—
	13	64.5	27.2	42.2	—	—	—	—
J.S.	8	74.5	45.8	61.5	17.5	23.5	38.3	51.4
N.T.	4	56.9	36.2	63.6	15.4	27.1	20.8	36.6

*Day of onset approximated.

Results. ANTIPYRINE SPACE. The initial antipyrine space was greater than 60% of the body weight in 6 of the 8 patients (Table 2). The other 2 patients, both women, had antipyrine spaces of 46.5% and 46.1% respectively. The former of these 2 had had a hypophysectomy for carcinoma of the breast and was receiving steroids; the latter had additional studies performed within the following 8 days and the changes in antipyrine space paralleled (within the experimental error of the method) the changes in body weight. Three of the patients survived, all of whom had an initial antipyrine space greater than 60%. In each case the antipyrine space decreased markedly during convalescence and after recovery (Fig. 1). When the plasma disappearance curves for antipyrine were examined, it was noted that although antipyrine disappeared at a slower rate from the plasma during the oliguric

TABLE 3.—SLOPES OF ANTIPYRINE AND RADIOSULFATE PLASMA DISAPPEARANCE CURVES

	Oliguric Phase		*Convalescent and post convalescent studies*	
Pt.	*Antipyrine m x 10⁻³*	*Radiosulfate m x 10⁻³*	*Antipyrine m x 10⁻³*	*Radiosulfate m x 10⁻³*
H.F.	103.98	−1.07	—	—
E.T.	20.73	0.93	—	—
L.G.	40.14	−0.62	58.20 46.15	37.39 33.83
V.A.	55.30	0.80	32.21 88.30	23.82 17.58
M.S.	8.39	−1.98	39.27 42.20 42.85	19.98 25.07 35.12
M.Z.	27.79	−3.20	—	—
	48.08	—	—	—
	29.78	—	—	—
	35.67	—	—	—
J.S.	32.27	0.16	—	—
N.T.	24.63	−0.43	—	—
Mean	38.80	−0.68	49.9	27.5
Standard deviation	25.3	1.2	18.7	7.8

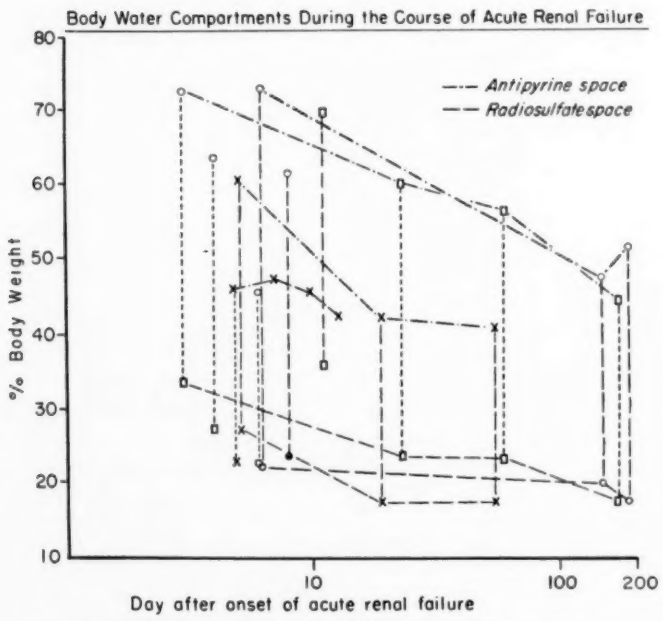


Fig. 1.—Body water compartments during the course of acute renal failure.

phase than during the convalescent or postconvalescent period, the differences in rate were not significant (Table 3 and Fig. 2).

RADIOSULFATE SPACE. All of the patients had a radiosulfate space greater than 20% of the body weight, and in the 3 patients who survived, the radiosulfate space decreased to 17.4%, 17.8%, and 18.1% of the body weight respectively. Examination of the plasma disappearance curve of radiosulfate revealed an interesting phenomenon. In clinically healthy individuals the plot

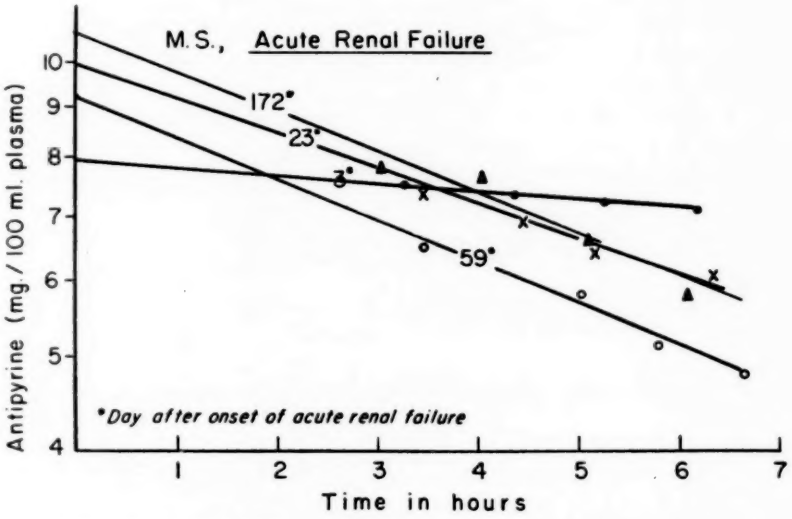


Fig. 2.—Patient M.S.: Antipyrine plasma disappearance curves.

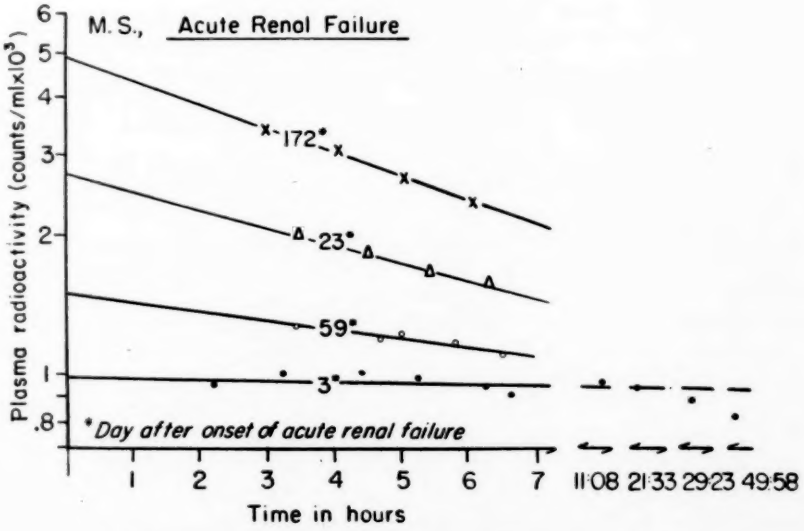


Fig. 3.—Patient M.S.: Radiosulfate plasma disappearance curves.

of plasma counts does not parallel the plot of counts remaining in the body, the latter being derived by the formula: (total number of counts injected) — (counts excreted in the urine) = (counts remaining in the body), but decreases at a faster rate indicating loss of radiosulfate into sinks other than the urine (Explanatory Note). In contrast to these observations there was no appreciable disappearance of radiosulfate from the radiosulfate space during the oliguric phase in our patients (Table 3, Fig. 3) as illustrated by M.Z. in whom there was no appreciable loss of radiosulfate during an observation period of 200 hours (Fig. 4). When the rate of disappearance of the derived plasma curves for radiosulfate (*Explanatory Note* below) during the convalescent and postconvalescent periods was compared to the rate of the disappearance of radiosulfate from the plasma during the oliguric phase for all the patients, it was found that the difference was highly significant ($t^2>92$, $p<0.001$).

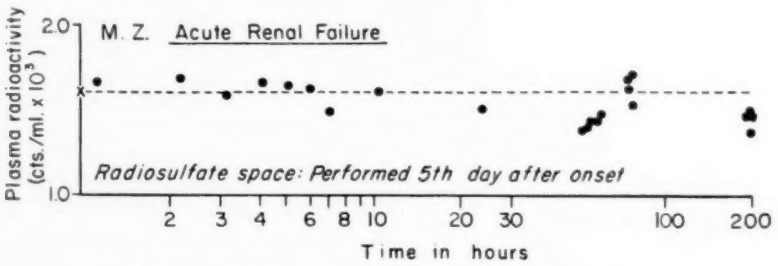


Fig. 4.—Patient M.Z.: Radiosulfate plasma disappearance curve.

RENAL HEMODYNAMICS. C_{In} and C_{PAH} were markedly reduced in the immediate postoliguric phase and subsequently, recovery toward normal values occurred (Table 4). The increase in C_{In} did not parallel the increase in C_{PAH} as demonstrated by the variable filtration fraction in M.S. The administration of acetazolamide and pitressin did not produce any significant change in C_{In} or C_{PAH}. The administration of tetra-ethyl-ammonium chloride (TEAC) produced a decrease in C_{In} and C_{PAH} during the diuretic phase.

WATER EXCRETION. The early diuretic phase was characterized by a low fixed urine flow and the water excreted represented a large portion of the filtered water load. Administration of acetazolamide and pitressin to patient M.S., when C_{In} was less than 10% of normal, did not produce any significant change in the % filtered water load excreted; however, when there was an increase of C_{In} to a range 20 to 30% of normal, there was a significant increase in the % of filtered water load excreted after the administration of acetazolamide ($P<0.01$). During subsequent studies, when C_{In} was approximately 50% normal or greater, administration of acetazolamide produced an increase in the urine flow and % filtered water load excreted and pitressin produced a decrease in the urine flow and % filtered water load excreted.

ELECTROLYTE EXCRETION. When C_{In} was less than 10% normal, the % filtered sodium and potassium load excreted was markedly elevated (Table 4). The administration of acetazolamide produced a significant increase in the % filtered potassium load excreted ($P<0.05$); however, a significant increase in the % of filtered sodium load ex-

creted was not demonstrated. If the acetazolamide and pitressin periods were considered together and compared to the control period, then a significant increase in % filtered sodium load excreted was demonstrable ($P<0.01$). All studies showed significant changes in the excretion of % filtered load of sodium and potassium following the administration of acetazolamide after the C_{In} had increased to above 20% of normal (Fig. 6).

Discussion. ANTIPYRINE AND RADIOSULFATE SPACES. According to Steele and his co-workers[18], the range of antipyrine space for normal men is 40 to 68% of the body weight and for normal women is 30 to 53% of the body weight. By these criteria, 5 of our 8 patients had an excess amount of water in their body. Two mechanisms may account for this observation: (a) Excessive fluid administration, and (b) catabolism of body tissue with release of

Explanatory Note. In the clinically healthy subject, radiosulfate is lost into sinks other than the urine as demonstrated by the difference in slope between the curve of plasma radioactivity and the curve of radioactivity remaining in the body (Fig. 5).

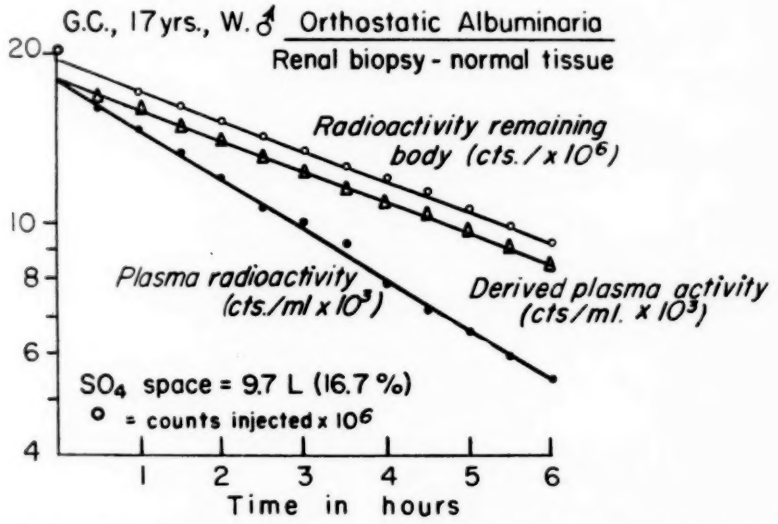


Fig. 5.—Radiosulfate plasma disappearance curve and derived plasma activity in a clinically healthy subject.

A plasma disappearance curve may be derived for the case of zero extra renal clearance by the following formula:

$$P'_t = \frac{R_t}{S_o}$$

where:

R_t = amount of radiosulfate remaining in the body at time t in counts/minute = amount of radiosulfate injected − amount of radiosulfate excreted in the urine

S_o = "zero time" radiosulfate space in ml.

P'_t = derived plasma concentration in counts/minute/ml.

TABLE 4.—RENAL FUNCTION STUDIES

Patient	*M.S.*							
Day after onset	*9 (5)**			*16 (12)**			*21 (17)**	
Experimental Procedure	*Control*	*Acet-azolamide*	*Pitressin*	*Control*	*Acet-azolamide*	*Pitressin*	*Control*	*Pitressin*
Inulin	8.2	8.8	8.7	30	36	32	45	46
Clearance	8.2	8.4	8.7	34	31	33	55	50
ml./min./1.73 M2	7.6	8.6	10.5	32	31	32	54	55
			9.3					
Para-aminohippu-	71	77	77	144	189	164	382	365
rate	70	81	76	164	163	165	429	397
Clearance	68	80	86	165	167	166	444	421
ml./min./1.73 M2			76					
	0.12	0.11	0.11	0.21	0.19	0.20	0.12	0.13
Filtration	0.12	0.11	0.12	0.21	0.19	0.20	0.13	0.13
Fraction	0.11	0.11	0.12	0.19	0.19	0.20	0.12	0.13
			0.12					
	2.4	2.5	2.6	1.4	2.2	2.5	6.7	4.0
Urine Flow	2.4	2.7	2.7	1.3	2.5	2.1	8.7	1.0
ml./min	2.2	2.6	3.2	1.3	2.7	2.1	7.0	1.2
			2.9					
Water	37	36	38	5.7	7.5	9.6	18.5	11.0
Excretion	37	40	39	4.9	10.0	8.1	19.9	2.5
% Filtered	37	49	38	5.2	10.1	8.1	16.1	2.8
load			39					
Sodium	265	307	330	203	326	316	149	147
Excretion	270	321	341	215	348	311	177	138
microequivalents/min	268	328	406	224	332	329	176	168
			376					
Sodium	31.3	32.9	36.1	6.3	8.5	9.3	3.0	3.0
Excretion	31.6	36.0	36.5	6.1	10.6	8.9	3.0	2.6
% Filtered	33.9	36.4	36.0	6.7	10.1	9.5	3.0	2.8
load			37.5					
Potassium	25.4	32.4	30.7	43	63	92	30	39
Excretion	25.7	37.2	45.6	45	73	118	37	75
microequivalents/min	25.7	36.8	45.2	45	72	98	39	59
			39.7					
Potassium	155	202	197	31	43	76	17	24
Excretion	169	242	281	30	60	96	18	42
% Filtered	187	238	241	35	61	81	19	30
load			234					
Maximal Specific Gravity (concentration) test	1.010			1.012			1.019	

*N_1 (N_2)
N_1 = of oliguria
N_2 = of diuresis

water of oxidation and preformed water. As mentioned previously, the daily fluid intake of these patients, prior to our observation, was determined by the formula, intake = 24-hour urine output plus one liter. This intake could not account for the excess of water present in our patients who survived. We believe our data support the second mechanism. Our direct measurements of total body water give values much larger than those derived indirectly by means of the balance technique by Bleumle, Potter, and Elkinton[3]; however, these authors have emphasized the uncertainty of their calculations of absolute values of body constituents and our data support their discussion.

The uniform increase in radiosulfate space provides an explanation for the frequent appearance of pulmonary edema in these patients. Denko and Priest[6] have shown that radiosulfate is incorporated into a wide variety of human tissue. Our observation of a decreased rate of disappearance of radiosulfate from the plasma during the oliguric phase supports the hypothesis of a predominant catabolic response

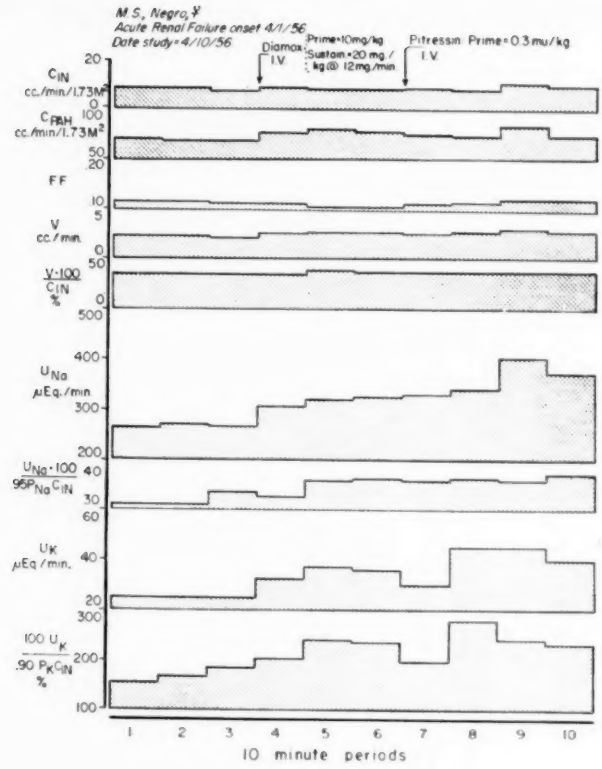
TABLE 4.—RENAL FUNCTION STUDIES (*Continued*)

21(17)°		V.A. *13(4)°*		*20(11)°*			*52 (43)°*		L.G. *147 (141)°*	
Acet-azolamide	*Recovery*	*Control*	*Acet-azolamide*	*Control*	*Acet-azolamide*	*TEAC*	*Control*	*Acet-azolamide*	*Control*	*Acet-azolamide*
46	39	21	25	65	77	43	105	117	93	100
40	45	26	19	66	50	45	103	81	79	80
45	41	24	19	57	52	45	113	85	101	69
			21							85
418	359	204	192	468	512	315	565	696	440	545
405	389	186	163	480	466	330	558	548	375	508
437	356	175	149	399	410	333	586	511	472	398
			167							476
0.11	0.11	0.10	0.13	0.14	0.15	0.14	0.19	0.17	0.21	0.18
0.10	0.12	0.14	0.12	0.14	0.11	0.14	0.18	0.15	0.21	0.16
0.10	0.12	0.14	0.13	0.14	0.13	0.14	0.19	0.17	0.21	0.17
			0.12							0.18
1.8	4.6	2.0	3.6	0.7	1.3	1.4	6.2	10.6	6.3	8.2
4.0	1.9	2.4	3.6	0.9	1.3	1.3	7.1	6.8	1.8	8.5
6.3	1.8	2.3	3.7	0.7	1.2	1.3	5.7	5.5	1.3	4.1
			3.7							5.1
4.9	14.9	11.6	17.2	1.3	2.0	4.0	7.2	11	7.0	8.6
12.4	5.4	11.4	22.2	1.6	3.3	3.6	8.5	10	2.4	11.0
17.6	5.4	11.7	22.8	1.6	2.9	3.5	6.1	8	1.4	6.3
			20.9							6.3
258	290	67	166	51.5	255	140	131	551	42	314
327	303	82	189	61.8	276	109	128	523	26	349
337	309	83	181	61.1	266	116	135	519	41	287
			120							389
5.2	7.5	2.8	5.8	.7	3.1	3.1	1.1	4.3	0.34	2.4
7.6	6.7	2.9	8.6	.9	5.2	2.2	1.1	5.9	0.25	3.3
6.9	7.5	8.1	8.6	1.0	4.8	2.3	1.1	5.6	0.31	3.2
			5.0							3.5
64	83	29	75	29	112	155	28	148	60	240
86	92	35	77	32	146	116	37	209	60	333
82	74	34	75	29	148	117	37	210	74	266
			77							313
38	70	68	169	18	62	162	9	49	18	71
55	67	77	220	21	126	118	14	101	22	132
52	58	72	215	21	122	118	13	101	21	123
			200							116
		1.011		1.014			1.029		1.029	

during the course of acute renal insufficiency. However, the constant radiosulfate space which we observed contrasts with the progressive increase in inulin space demonstrated by Finkenstaedt, O'Meara and Merrill[7] and suggests the inulin is metabolized, an observation demonstrated in normal subjects by Deane and Smith[5]. Our failure to find any significant extra renal clearance of radiosulfate from the plasma during the oliguric phase is in contrast to the observations of Smith, Madisso, and Pitts[17] in nephrectomized dogs. At this time, it is not clear whether this is due to the fact that the nephrectomized dog is not the experimental analogue of the paient with acute renal failure, or that this represents a species difference in response to acute uremia.

RENAL HEMODYNAMICS. Our measurements of inulin clearance, para-aminohippurate clearance and specific gravity of urine conform to the pattern described by Sirota[14].

WATER AND ELECTROLYTE EXCRETION. The data indicate that the patient suffering from acute renal failure has functioning renal tubular cells which are able to respond, with respect to sodium and potassium excretion, to a carbonic anhydrase inhibitor in a manner similar to that of normal tubules


M S., Negro, ♀
Acute Renal Failure onset 4/1/56
Date study = 4/10/56
Diamox I.V.
Prime = 10 mg/kg
Sustain = 20 mg./kg @ 12 mg./min
Pitressin Prime = 0.3 mu/kg I.V.
C IN cc./min/1.73M²
C PAH cc./min/1.73M²
FF
V cc./min.
V·100 / C IN %
U Na µEq./min.
U Na · 100 / 95 P Na C IN
U K µEq./min.
100 U K / .90 P K C IN %
1 2 3 4 5 6 7 8 9 10
10 minute periods

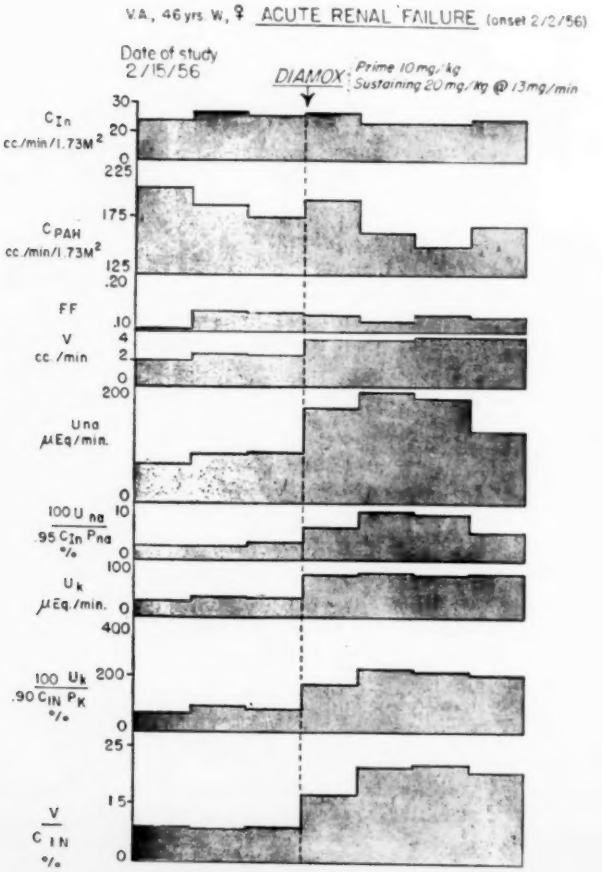

V.A., 46 yrs. W, ♀ ACUTE RENAL FAILURE (onset 2/2/56)
Date of study 2/15/56
DIAMOX: Prime 10 mg./kg Sustaining 20 mg./kg @ 13 mg./min
C In cc./min/1.73M²
C PAH cc./min/1.73M²
FF
V cc./min
Una µEq./min.
100 U na / .95 C In P na %
U k µEq./min.
100 U k / .90 C IN P K %
V / C IN %

Fig. 6.—Renal function studies.

(Berliner and Orloff[2]). Our data also confirm the observation of Baldwin and his colleagues[1] that the response of the tubule of the patient, with acute renal failure, to an antidiuretic stimulus is impaired; however, in our patients a response may have been precluded by the evident osmotic diuresis. We are not able to discriminate between the following mechanisms to explain our observations: (1) A few nephrons are spared by the primary precipitating factor and function normally or (2) all nephrons have been affected by the primary precipitating factor but individual cells have been spared.

Conclusions. The marked increase in total body water in the majority of our patients and the uniform expansion of the extracellular fluid volume in all of our patients demonstrates the need for rigid restriction of water and sodium during the oliguric phase and restriction of water during the diuretic phase. Any attempt to administer water in volume equal to urine output during the diuretic phase only prolongs the diuretic phase (Swan and Merrill[19]). In addition, supplemental electrolytes should be administered only on clinical indication during the diuretic phase.

Summary. 1. Serial measurements of antipyrine and radiosulfate spaces were made in 8 patients with acute renal insufficiency. In 3 patients who recovered, serial acute studies of the effect of acetazolamide and pitressin upon renal hemodynamics and sodium, potassium, and water excretion were made.

2. The initial antipyrine space was greater than normal in 5 of the 8 patients. In 3 patients who survived, the initial antipyrine space was greater than normal and decreased significantly during convalescence and after recovery.

3. The initial radiosulfate space was greater than normal in all of the patients; in 3 patients who survived, it decreased significantly. In addition, there was no appreciable extra renal clearance of radiosulfate from the plasma during the oliguric phase of the illness.

4. A significant increase in sodium and potassium excretion was demonstrated following the administration of acetazolamide during the early diuretic phase.

5. The application of these data to the treatment of acute renal failure is discussed.

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(Interlingua on page 189)

SUMMARY IN INTERLINGUA

(See page 201 for original article)

Le Action Clinic E Cerebral De Promethazina E De Hydrochloruro De Methylphenidato

Le effectos metabolic clinic e cerebral de administrationes intravenose de promethazina esseva determinate in patientes con augmentate activitate psychomotori. Simile studios esseva etiam effectuate post le administration de hydrochloruro de methylphenidato a patientes qui habeva previemente recipite injectiones de promethazina. Le injection intravenose de promethazina resultava in un stato de sedation profunde ab que le patiente non poteva esser extrahite.

Le administration de promethazina esseva associate con un reduction del total fluxo de sanguine e del consumption de oxygeno in le cerebro e con un augmento del resistentia in le vasos cerebral e del valor medie del pression cerebro-arterial. Hydrochloruro de methylphenidato non exerceva un influentia appreciabile super le effectos clinic o super le effectos experimental que habeva essite inducite per promethazina.

Le datos suggere que promethazina, per contrasto con le altere derivatos de phenothiazina, induce, post su injection intravenose in relativemente forte concentrationes, un depression del centros tanto cortical como etiam subcortical. In vista de iste action, il pare que le droga debe haber un considerabile valor therapeutic in le tractamento de patientes con augmentate activitate psychomotori in qui un regulation clinic non es effectuabile per promazina o per chlorpromazina.

THE CLINICAL AND CEREBRAL ACTION OF PROMETHAZINE AND METHYLPHENIDATE HYDROCHLORIDE*

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The phenothiazine derivatives, chlorpromazine and promazine, have been demonstrated to be of considerable value in the symptomatic management of increased psychomotor activity accompanying various psychotic states, as well as the alcohol-withdrawal syndromes (Fazekas *et al.*[3,4]). Promethazine, an isomer of promazine, is used therapeutically as an antihistaminic (Halpern and Hamburger[5]) and as a premedicant for anesthesia (Sadove[9]). The close similarity in chemical structure between the two drugs, and particularly their recognized central nervous system effects, suggested that the isomer, if administered intravenously in larger concentrations than heretofore employed, might also be of value in controlling increased psychomotor activity associated with various clinical disturbances.

In the present study, the effectiveness of promethazine in controlling increased psychomotor activity of acutely disturbed subjects, as well as its influence on cerebral hemodynamics and oxygen utilization, was determined. In a number of these subjects, the effectiveness of methylphenidate hydrochloride (a new analeptic) in reversing the central nervous system depressant action induced by promethazine was also evaluated clinically and experimentally.

Method. Promethazine was administered intravenously in doses ranging from 200 to 400 mg. to 27 patients with delirium tremens and to 18 acutely disturbed subjects with various psychoses. The total dose was administered within a period of from 5 to 10 minutes, and the patients were observed for changes in behavior and state of consciousness. Blood pressure was recorded in most

*This investigation was supported by a research grant (PHS B–178) from the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service.

The promethazine (Phenergan) used in this study was supplied by Wyeth Laboratories, Inc., Philadelphia. The methylphenidate hydrochloride (Ritalin) was supplied by Ciba Pharmaceutical Products, Inc., Summit, N.J.

instances before and within one-half hour after the administration of the drug.

The influence of promethazine on cerebral blood flow, vascular resistance, mean arterial pressure, and total cerebral oxygen consumption was determined in 10 subjects. Cerebral studies were performed before and within 15 to 30 minutes after the intravenous administration of from 200 to 400 mg. of the drug. Seven of these subjects were given 400 mg. of methylphenidate hydrochloride intravenously (injection time, less than 5 minutes) 30 to 45 minutes after promethazine administration, and clinical observations were made of its effectiveness in overcoming the action of promethazine. In 3 agitated subjects, control experimental studies could not be made and cerebral studies were only performed following the administration of promethazine and after the injection of methylphenidate hydrochloride.

Scheinberg and Stead's modification[10] of Kety and Schmidt's procedure[6] for the determination of cerebral blood flow was applied in this study. The gas mixtures utilized were those described by Kety and Schmidt[6]. The oxygen content of the blood was determined by the manometric technique of Van Slyke and Neill[7]. Mean arterial blood pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer (Alman and Fazekas[1]).

Results. Promethazine, in the concentrations employed, induced within 5 to 10 minutes after its intravenous administration a deep state of sedation from which the patient could not be aroused by external stimuli. The patients frequently coughed for a brief period immediately after the rapid injection was started, a phenomenon also noted after the injection of other phenothiazine derivatives.

In all subjects there was a transient excitatory phase immediately following the injection which persisted usually for only 1 to 2 minutes and was characterized by myoclonic-like involuntary motor activity. In 5 of the subjects initially given 100 to 150 mg. of promethazine, there was a marked increase in psychomotor activity and intensification of their disturbed mental state. The additional administration of from 100 to 200 mg. of promethazine was shortly followed by a cessation of the excitatory phase and the induction of a deep state of sedation. Sedation, once induced, persisted for 4 to 6 hours and was usually followed by a return of the increased psychomotor activity. The subsequent administration of equivalent concentrations of promethazine previously given would again induce a quiescent state persisting for approximately the same period of time. With continued administration of the drugs, the patients with delirium tremens could be kept sedated until their delirious state had spontaneously subsided. In only 2 of the psychotic subjects, was there improvement of their mental state following repeated induction of promethazine-induced sleep. Even though 5 of the alcoholic subjects had a grand mal seizure within 24 to 48 hours prior to the injection of promethazine, seizures were not observed in any of these subjects following the administration of promethazine. There was a moderate rise in both diastolic and systolic pressure which persisted for approximately 30 minutes following the injection of promethazine. In no instance was there a significant reduction of pressure frequently observed after the administration of the phenothiazine derivatives.

In a number of the subjects, venous thrombosis was noted following the repeated injection of promethazine into the same vessel. This complication was obviated either by diluting the drug (200 mg. in 5 ml.) or by injecting the drug slowly (25 mg. per min.). A similar irritating effect on vascular structures has been noted following the administration of chlorpromazine and promazine. Methylphenidate hydrochloride in the concentrations employed was not effective in arousing the patients previously sedated with promethazine.

Table 1 presents the cerebral hemodynamic and metabolic data obtained on 10 patients before and after the intravenous administration of from 200 to 400 mg. of promethazine. The results demonstrate a significant decrease in the rate of total cerebral blood flow and oxygen consumption and an increase in mean arterial pressure and cerebral vascular resistance following the administration of promethazine.

Discussion. It is interesting that despite the similarity in chemical structure, the clinical-experimental effects of promethazine are different in some respects than those induced by promazine. Both drugs, when administered in adequate concentrations, will usually induce a quiescent state in patients with increased psychomotor activity; not accomplished by the administration of this analeptic agent.

TABLE 1.—THE INFLUENCE OF PROMETHAZINE ON CEREBRAL HEMODYNAMICS AND METABOLISM

		CBF		*$CMRO_2$*		*CVR*		*MAP*		*AVO_2*		
Subj.	*Age*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*Promethazine I.V. (mg.)*
1	23	78.1	65.3	3.5	3.1	1.1	1.9	83	124	4.53	4.73	300
2	45	53.9	39.3	3.8	2.9	1.8	3.1	97	120	7.01	7.49	350
3	30	53.3	34.7	3.3	2.6	1.8	3.7	98	129	6.12	7.55	375
4	38	53.6	39.9	2.8	2.6	1.7	3.0	93	118	5.20	6.48	300
5	38	71.6	44.2	3.3	2.3	1.1	2.6	77	116	4.57	5.19	400
6	32	52.0	37.6	2.5	1.8	2.1	3.1	110	117	4.82	4.78	300
7	31	33.5	35.7	1.1	1.2	2.7	3.4	91	120	3.16	3.43	400
8	45	50.3	34.4	3.7	3.0	2.2	3.7	113	126	7.26	8.68	200
9	50	39.7	33.1	2.9	2.8	2.1	3.9	85	129	7.23	8.33	200
10	38	50.9	33.1	2.1	1.6	1.8	3.8	90	127	4.19	4.96	275
						Mean Values						
	37	53.7	39.7*	2.9	2.4*	1.8	3.2*	94	123*	5.41	6.12*	310

CBF signifies cerebral blood flow in ml./100 gm. of brain/min.; $CMRO_2$, cerebral oxygen consumption in ml./100 gm. of brain/min.; CVR, cerebral vascular resistance in mm. of Hg/ml. blood/100 gm. of brain/min.; MAP, mean arterial blood pressure in mm. of Hg; AVO_2, cerebral arteriovenous oxygen difference in volumes per cent; C, control; and E, experimental.

*Significant difference, $p<.05$.

In Table 2 are presented the cerebral hemodynamic and metabolic findings after the administration of methylphenidate hydrochloride to 10 subjects (200 mg. to 1 subject and 400 mg. to 9) who were previously sedated with from 250 to 400 mg. of promethazine. The data demonstrate a reduction in the rate of cerebral blood flow following administration of methylphenidate hydrochloride but no change in cerebral oxygen utilization, mean arterial pressure, or cerebral vascular resistance. As previously mentioned, arousal was the depth of sedation noted after promethazine is more marked, however, than that observed following promazine. After the latter drug, patients can be readily aroused by external stimuli; whereas after promethazine, arousal cannot be accomplished, and the sedation induced resembles that of barbiturate sedation. It should also be mentioned that patients with delirium tremens previously observed to be resistant to promazine were rendered unconscious by the administration of

equivalent concentrations of promethazine.

Previous studies have demonstrated that methylphenidate hydrochloride in smaller concentrations than currently administered was effective in arousing the patient rendered quiescent with promazine (Ehrmantraut *et al.*[2]); whereas in patients sedated with promethazine, this drug in the concentrations employed had no arousal action. These observations suggest that promazine has not been demonstrated (Ehrmantraut *et al.*[2]). Promazine, unlike promethazine, presumably exerts its effects by primarily inhibiting the utilization of adenosinetriphosphate, particularly by subcortical centers.

In view of the observed increase of mean arterial pressure, the reduction in cerebral blood flow noted after promethazine can most likely be attributed to the fall in the oxygen requirements of the brain. Unlike other phenothiazine derivatives which, presumably because of their ganglioplegic action, may occasionally induce a reduction of blood pressure (Rea, Shea and Fazekas[8]), promethazine administration is frequently associated with a moderate rise in blood pressure. The reason for the temporary increase in pressure is not evident but may result from activation of central sympathetic centers since excitation was observed in a number of our cases which resembled a release-type of phenomenon

TABLE 2.—THE INFLUENCE OF METHYLPHENIDATE HYDROCHLORIDE ON THE CEREBRAL HEMODYNAMICS AND METABOLISM OF PATIENTS GIVEN PROMETHAZINE

		CBF		*$CMRO_2$*		*CVR*		*MAP*		*AVO_2*		*Promethazine*	*Methylphenidate*
Subj.	*Age*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*C*	*E*	*I.V. (mg.)*	*I.V. (mg.)*
1	23	65.3	51.8	3.1	3.1	1.9	2.4	124	126	4.73	5.92	300	400
2	45	39.3	31.9	2.9	3.0	3.1	3.7	120	118	7.49	9.42	350	400
3	30	34.7	28.6	2.6	2.6	3.7	4.5	129	129	7.55	8.99	375	400
4	38	39.9	36.0	2.6	2.5	3.0	2.0	118	73	6.48	6.90	300	400
5	38	44.2	39.8	2.3	2.2	2.6	2.3	116	93	5.19	5.52	400	400
6	32	37.6	42.5	1.8	2.5	3.1	2.8	117	118	4.78	5.89	300	400
7	31	35.7	22.0	1.2	1.0	3.4	5.1	120	113	3.43	4.41	400	400
8	31	43.8	40.1	2.2	2.5	2.5	2.3	108	93	5.10	6.31	250	200
9	37	42.4	38.2	2.6	2.5	2.9	3.1	121	118	6.09	6.55	250	400
10	23	36.7	34.5	3.1	3.0	3.0	3.1	110	107	8.42	8.82	400	400
						Mean Values							
	33	42.0	36.5*	2.4	2.5	2.9	3.1	118	109	5.93	6.87*	332	380

CBF signifies cerebral blood flow in ml./100 gm. of brain/min.; $CMRO_2$, cerebral oxygen consumption in ml./100 gm. of brain/min.; CVR, cerebral vascular resistance in mm. of Hg/ml. blood/100 gm. of brain/min.; MAP, mean arterial blood pressure in mm. of Hg; AVO_2, cerebral arteriovenous oxygen difference in volumes per cent; C, control (values after administration of promethazine); and E, experimental (values after administration of methylphenidate).

*Significant difference, $p<.05$.

occasionally observed after the administration of barbiturates.

Summary. The clinical and cerebral metabolic effects of intravenously-administered promethazine was determined in patients with increased psychomotor activity. Similar studies were also made after the administration of methylphenidate hydrochloride to patients previously given promethazine. The intravenous injection of promethazine resulted in a deep state of sedation from which the patient could not be aroused.

The administration of promethazine was associated with a decrease in total cerebral blood flow and oxygen consumption and an increase in cerebral vascular resistance and mean arterial pressure. Methylphenidate hydrochloride did not appreciably influence either the clinical or experimental effects induced by promethazine.

The data suggest that promethazine, unlike other phenothiazine derivatives, when administered intravenously in relatively large concentrations may induce a depression of both cortical and subcortical centers. In view of this action, the drug would seem to have considerable therapeutic value in the management of those patients with increased psychomotor activity not clinically controlled by either promazine or chlorpromazine.

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(Interlingua on page 200)

PROGRESS
OF
MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF

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CLINICAL SIGNIFICANCE OF MAGNESIUM DEFICIENCY AND ITS RELATION TO PARATHYROID DISEASE

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AND

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THE importance of magnesium in the mineral metabolism of the body is currently receiving increased attention. Extensive reviews of magnesium metabolism in health and disease have appeared in recent years[12,14,15,25,36]. In the present report no attempt will be made to summarize the abundant literature, but merely to cite work pertinent to the interpretation of the cases reported in the present article.

Magnesium is divalent cation with an atomic weight of 24 and an atomic number of 12. It is the second of the alkaline earth metals in the periodic table of the elements while calcium is the first. The body contains approximately 20 gm. of magnesium, of which the greater part is found in muscle and bone[25]. Recent methods of determination have established that normal serum concentrations of the ion range between 1.8 and 2.2 mg. per 100 ml.[25]. The widest range of normal values reported, including the older techniques of analysis, is 1.7 to 3.0 mg. per 100 ml.[14]. There is little information on the urinary excretion of magnesium in healthy adults, but it is believed to average 150 mg. per 24 hours[42]. The ion is of physiologic importance. In addition to its effects on the neuro-

muscular system, magnesium is implicated in the activity of numerous enzymes, such as adenosintriphosphatase, hexokinase, and phosphoglucomutase.

The classic experiments of Loeb[23] on neuromuscular activity were among the first to demonstrate the physiological effects of magnesium. As a result of his investigations Loeb developed the thesis that the irritability of living tissue depends upon the various ions in the ambient fluid, particularly the metal ions, Ca, Na, K, and Mg. This led to the formulation of the so-called Loeb equation[36]; neuromuscular irritability is proportional to

$$\frac{Na^{+} + K^{+} + OH^{-}}{Ca^{++} + Mg^{++} + H^{+}}$$

An increase in the concentration of any ion in the numerator, or a decrease in the concentration of any ion in the denominator results in increased neuromuscular irritability.

The first impressive demonstration of the profound effects of magnesium deprivation in animals was the work of Kruse, Orent and McCollum[19,20,21,22,32]. Carefully controlled studies revealed that growing rats maintained on severely deficient magnesium diets developed marked hyperirritability to various stimuli with convulsions, rigidity and spasm leading to respiratory paralysis and death. The neurologic findings in these animals closely resembled symptoms seen in human cases of tetany. The abnormalities in these animals were directly related to the magnesium deprivation. All electrolyte values measured were normal, except for magnesium. Total and ultrafilterable calcium in the serum remained above limits considered to be the threshold for low calcium tetany (8 mg. and 2.5 mg. per 100 ml. respectively). The concentration of serum magnesium, however, showed profound decreases, particularly in the ionized fraction. These abnormalities were reversed by restoration of magnesium to the diet. This work was largely confirmed by other workers[41].

In sharp contrast to the well established findings in the animal work, clinical reports of the occurrence of symptomatic magnesium deficiency have been quite conflicting. Hirschfelder and Haury[18] in 1934 reported 6 patients who had convulsions and muscular twitchings during periods of hypomagnesemia. Serum calcium levels in these patients were above the tetany threshold. Remission of symptoms was obtained by oral administration of $MgSO_4$. Miller[29] in 1944 indicted hypomagnesemia as the cause of symptoms in a case of tetany of the newborn, and reported gratifying therapeutic results with the oral use of $MgSO_4$. Serum magnesium has been reported below normal in cases of infantile tetany, but serum calcium was also significantly reduced in these patients[7].

In an extensive review of magnesium metabolism in 1952, however, Martin, Mehl, and Wertman[25], criticized these previous reports of low magnesium tetany for lack of sufficient data to warrant conclusive interpretation of the role of low magnesium in the production of neurologic symptoms. They pointed out that information on acid base equilibrium is particularly important to rule out the known possibility that alkalosis has produced sufficient depression of the ionized fraction of serum calcium to produce tetany on that basis alone. They studied a number of cases in which hypomagnesemia occurred in association with a wide variety of disease states and found no symptoms directly attributable to low magnesium in any of these cases. This was surprising to them in view of the clear cut demon-

strations in animals that neurologic disturbances are associated with a significant magnesium depletion. They felt that the explanation for the discrepancy might be that despite the hypomagnesemia sufficient total body depletion of magnesium had not occurred in these individuals to produce the symptoms of magnesium deficiency.

Recently other reports have reaffirmed the belief that magnesium deficiency is clinically significant. Hypomagnesemia in association with bizarre neurologic disturbances has been reported in a large group of patients who had a long history of reduced intake of magnesium. Flink and co-workers[9] reported their findings in 33 such patients. Three patients in this group had been maintained for several weeks on magnesium-free parenteral fluids, while the other patients in the series were 30 alcoholics who showed the neurologic symptoms characteristic of delirium tremens. They displayed tremor and mental confusion and there was some correlation between the severity of symptoms and the degree of hypomagnesemia. Generally those receiving $MgSO_4$ responded more quickly than the patients whose therapeutic regimen did not include extra magnesium. Perhaps the most impressive feature of their report was the finding that in 5 cases magnesium therapy initiated improvement when the clinical course was worsening on other forms of therapy. In these patients relapse occurred when magnesium administration was prematurely stopped, but prompt improvement again followed restitution of magnesium therapy. Suter and Klingman[39] reported similar findings in 12 patients.

Harmon[13] reported a case of parathyroid adenoma in a child who displayed neurologic signs including convulsions in association with magnesium deficiency. In addition to severe hypercalcemia serum magnesium levels were observed as low as 0.17 mEq./L. in the immediate postoperative period. Considerable improvement followed the use of parenteral $MgSO_4$ but probably due to the long period before diagnosis and definitive treatment there were irreversible neurological sequelae.

Our interest in the clinical significance of alterations in magnesium metabolism in hyperparathyroid patients was originally aroused by experiences with a patient who died in tetany 2 weeks after removal of a parathyroid adenoma. Normal serum calcium levels were maintained by vigorous calcium therapy but this did not relieve the symptoms. Magnesium values were not obtained in this patient. In retrospect, we have speculated on the possible relationship of disturbed magnesium metabolism and the death of this patient. Since becoming interested in magnesium metabolism we have also observed postoperative patients who developed tremor and mental confusion during prolonged use of magnesium free parenteral fluids. Serum magnesium determinations confirmed the suspicion of hypomagnesemia, while serum calcium in these patients was normal. Prompt improvement with rapid disappearance of the signs of increased neuromuscular irritability followed the addition of 3 gm. of $MgSO_4$ to the intravenous fluids. The findings in 2 patients with hyperparathyroidism having changes in magnesium metabolism are given below and serve as the basis of our discussion of symptomatic magnesium deficiency.

Case Reports. CASE 1. I.C., a 70-year-old white woman, was admitted to the medical service of the Hospital of the University of Pennsylvania on February 7, 1956. Her presenting complaints were anorexia, weight loss, constipation, dysuria and vaguely localized back pain. On the day prior to admission the patient was febrile and suffered severe chills. She had had several previous admissions. In

1954 she was admitted with symptoms of chest pain, urinary frequency, and pain in both knees. Roentgen-ray examination of the chest showed collapse of the right middle lobe without evidence of active disease. A bone survey showed generalized decalcification with an isolated cystic area in the left femur. After extensive examination she was discharged without a primary diagnosis. In December, 1955, she was again admitted to the Medical Service with symptoms of general weakness, lower abdominal pain, urinary frequency and dysuria. Her blood urea nitrogen was elevated to 38 mg. per 100 ml. Urine culture revealed a hemolytic staphylococcus, coagulase positive. She was treated with penicillin and streptomycin. Her discharge diagnosis was cystitis and asymptomatic interatrial septal defect.

The admission physical examination showed a small, emaciated, acutely ill, disoriented, female lying in bed with her knees flexed. Her rectal temperature was 103.4°, pulse 120 and regular, and her blood pressure was 100/50. She showed signs of extreme wasting. The thyroid gland was not palpable and there was no venous distention. There were fine rales at both lung bases. A grade II systolic murmur was heard in the fourth left interspace, parasternally, and a grade II systolic murmur which was not transmitted at the apex. There were no precordial thrills. There was abdominal distention with a palpable fecal mass extending from the cecum to the rectum and generalized muscle guarding with hypoactive peristalsis. Rectal examination confirmed the fecal impaction and pelvic examination was negative. Her leukocyte count was 14,300 per c.mm. with a normal differential. Urinalysis showed a trace of albumin, clumps of white blood cells, and a few red blood cells. A strain of *E. coli* sensitive to chloramphenicol was obtained from the urine. The blood urea nitrogen was now 21 mg. per 100 ml. Serum Na was 128 mEq./L., and serum K 2.8 mEq./L. The electrocardiogram showed right ventricular hypertrophy with first degree A–V heart block. Her stool did not show occult blood when tested with guaiac. Chest roentgenogram showed the same findings as on her previous admission. A survey abdominal film was normal except for the presence of feces throughout the colon. Subsequent studies revealed the serum calcium to be 18.7 mg. per 100 ml., serum phosphorus 2.3 mg. per 100 ml. and alkaline phosphatase 9.4 Shinawara units. Repeated determinations were confirmatory. Urinary excretion of calcium ranged between 0.63 and 0.47 gm. per 24 hours. Urinary phosphorus excretion ranged between 0.42 and 0.26 gm. per 24 hours. Proctoscopy, an upper gastrointestinal roentgenographic study, barium enema and intravenous urogram revealed no abnormalities. A bone survey again confirmed generalized decalcification without evidence of other cystic lesions. Serial magnesium determinations were done upon serum and urine and the serum magnesium ranged between 1.9 mg. and 1.7 mg. per 100 ml. Twenty-four hour urinary excretion of magnesium ranged between 17 and 59 mg. Magnesium was determined by a modification of the titan yellow method of Heagy[17,35].

Repeated electrocardiographic examinations showed sinus rhythm with frequent supraventricular premature beats, incomplete right bundle branch block, and a short QT interval all interpreted as compatible with hypercalcemia. Clinical interest centered on differentiating hyperparathyroidism and metastatic malignancy as the cause of the hypercalcemia before deciding to explore the neck for an adenoma. Renal phosphate reabsorption ranged between 83% and 78%, unlike the usual case of hyperparathyroidism. However, the absence of any positive clinical evidence of malignancy was supported by other studies which cast doubt on the diagnosis of metastatic malignancy. Cerebrospinal fluid calcium was 6.3 mg. per 100 ml. Serum electrophoresis showed no elevation of the alpha II or gamma globulin fraction. As a final step the therapeutic trial with one week of cortisone administration was undertaken for distinguishing hypercalcemia due to metastatic malignancy and sarcoidosis from the hypercalcemia of hyperparathyroidism. Serum calcium and magnesium remained unchanged after a one week program of daily administration of 200 mg. of cortisone. The decision was then made to explore her neck. A 2 × 3 cm. parathyroid adenoma was removed from the region of the left lobe of the thyroid. Her immediate postoperative recovery was uneventful. On the first postoperative day urinary excretion of magnesium fell to 4.0 mg. per 24 hours. As shown in Fig. 1 the excretion of magnesium remained at extremely low levels over the remaining period of observation. On March 15, the second postoperative day, the serum calcium was 12.2 mg. per 100 ml. and serum magnesium 2.03 mg. per 100 ml. By this time the patient started to eat a normal diet.

One week after operation she developed periodic spells marked by mental confusion, weakness, vertigo, fasciculations of the calf muscles, and clonic shaking of the limbs with

ankle clonus. Chvostek's sign was negative. These attacks occurred several times daily, lasted about one half hour, and cleared completely. Figure 1 shows the serum calcium and magnesium values during this period. On the first day of symptoms a serum calcium value of 9.8 mg. per 100 ml. was obtained. Vigorous supplementary calcium therapy was initiated despite the normal serum calcium value. Intravenous calcium gluconate failed to abort the attacks and no improvement was noted. Blood CO_2 values during this period ranged between 19.1 and 24.4 mEq./L. making alkalosis seem unlikely. Two days after the attack started, on March 24, a serum magnesium value of 0.78 mg. per 100 ml. was obtained. On March 26 the serum magnesium determination was 0.75 mg. per 100 ml. Parenteral magnesium therapy was, therefore, initiated. Two gm. of $MgSO_4$ were given intramuscularly on that day. On the following 2 days additional $MgSO_4$ was given; 4 gm. $MgSO_4$ were given intramuscularly and 1.5 gm. $MgSO_4$ intravenously. By March 28, in response to the intravenous therapy, calcium values had risen to 14.2 mg. and magnesium to 1.4 mg. per 100 ml. There was definite clinical improvement and between March 28 and April 2 no attacks were noted. However, on April 2 and again on April 6, the patient developed periods of confusion, vertigo, and weakness without signs of neuromuscular irritablity. Blood chemistry studies obtained with specimens obtained during these attacks were normal (on April 2 Ca was 8.8 mg., Mg 2.0 mg., and serum glucose 65 mg. per 100 ml. On April 6 Ca was 8.8 mg., Mg 1.94 mg., and glucose 70 mg. per 100 ml.). Her symptoms cleared completely on each occasion in about one-half hour without therapy. The remaining 6 days of the patient's hospital stay were uneventful and without recurrence of symptoms or further parenteral magnesium therapy.

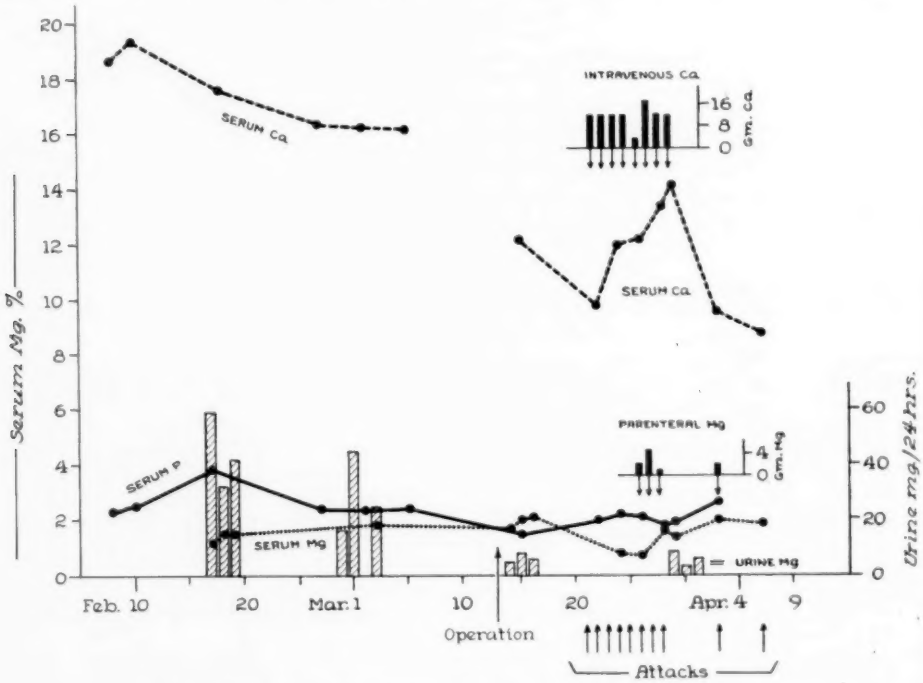

Fig. 1.—Calcium, phosphorus and magnesium findings in Case 1.

CASE 2. R.C., a 49-year-old white woman, was first admitted to the Hospital of the University of Pennsylvania on September 7, 1956, with a chief complaint of pain in both knees of 8-months' duration. Prior to admission, roentgenograms of the knees and two long bone survey examinations had been performed at another hospital. As a result of

these studies, she was referred to the University Hospital for possible surgery with a tentative diagnosis of hyperparathyroidism.

The pain in the knees was dull in character, and produced a slight limp. Her medical history and systemic review were noncontributory. Physical examination revealed a well developed, well nourished white woman in no acute distress. Nystagmus was noted on right lateral gaze. There was no adenopathy. The lungs were clear and there was no cardiac enlargement but a grade II systolic murmur was heard at the apex. Abdominal examination was negative. Tenderness was elicited by pressure over both knees, the tibias, and the left jaw. There was no costo-vertebral angle tenderness. Reflexes were hyperactive bilaterally with greater accentuation on the left side. No pathological reflexes nor sensory loss were noted.

Admission laboratory studies revealed a hemoglobin of 10.8 gm.% and a white blood count of 10,800 with a normal differential. The blood urea nitrogen was 15 mg. and the blood glucose was 109 mg. per 100 ml. Serum albumin was 4.0 gm.%, globulin 3.0 gm.%, K 4.4 mEq./L., Ca 18.2 mg. per 100 ml., phosphorus 2.3 mg. per 100 ml. and alkaline phosphatase 19.1 units. Urine specific gravity was 1.010 with a trace of albumin, rare red blood cells and 8 to 12 white blood cells per high power field (voided specimen). Kolmer and Kline tests on the blood serum were nonreactive. The intravenous urogram was normal as was the PSP excretion. Roentgenographic examination revealed generalized decalcification with subperiosteal resorption of the shafts of most of the phalanges and several of the metacarpals. There was a loss of the lamina dura. These changes were considered characteristic of hyperparathyroidism.

After an unproductive exploration of the neck, a 3 × 2 cm. parathyroid adenoma was found and removed from the anterior mediastinum overlying the pericardium. In the week following the removal of the tumor the serum calcium and phosphorus levels returned toward normal. Preoperatively a serum magnesium value of 1.86 mg. per 100 ml. had been obtained and urinary magnesium excretion had averaged 35 mg. per 24 hours. During the week between the negative exploration of the neck and the exploration of the mediastinum, urinary excretion of magnesium was not measured. In the postoperative period the collection of urine specimens was incomplete because of the occasional incontinence of the patient. For this reason the magnesium values are not charted as precise values cannot be given.

Beginning with the first postoperative day, urine excretion of magnesium fell to levels estimated (because of some loss) to be between 4.0 and 8.0 mg. per 24 hours. Serum magnesium was likewise consistently low in the postoperative weeks with values as low as 0.85 mg. per 100 ml. being observed. Four days after operation she developed a psychotic episode described by the psychiatrist as being an agitated depression with a large paranoid element. The patient experienced auditory hallucinations and displayed periods of catatonia and athetoid movements. Because of the low serum magnesium a single intravenous infusion of 5 gm. $MgSO_4$ was given on the first day of the attack but was without observable effect. Her symptoms gradually improved after 9 days of tranquillizing agents, in the form of pills and psychiatrists. She was discharged much improved on a program of vitamin D and supplementary calcium.

Discussion. Complete balance studies unfortunately were not obtained on these patients. Sufficient information was obtained, however, to note striking changes in their magnesium metabolism unlike anything previously reported to our knowledge. In both patients there was a marked and prolonged postoperative decrease in the excretion of magnesium in the urine despite an adequate intake.

The recent work of Moore[30] has shown that alterations in electrolyte metabolism occur following surgery. These effects are presumably mediated through the adrenal cortex as part of the stress response. In this connection Haynes' group[16] has studied urinary magnesium excretion under conditions of operative stress in a variety of surgical procedures. They found a definite but transient decrease in urinary excretion of magnesium after operation with subsequent rise in excretion after 5 days. ACTH administration to normal subjects produced similar results, relating the whole process to the stress reaction. In the subjects of Haynes' experiments reduction in urinary ex-

cretion of magnesium was accompanied by a reciprocal rise in serum magnesium levels, suggesting that the change in magnesium metabolism was primarily a retention of this ion in extracellular fluid.

These findings are quite different from our observation concerning magnesium metabolism in patients with hyperparathyroidism. The extent and duration of the decrease in urinary magnesium excretion following the removal of the adenoma suggests a qualitatively different mechanism. In the hyperparathyroid patients magnesium excretion fell almost to zero and remained at low levels during the several weeks of postoperative studies. Furthermore, serum magnesium levels also decreased despite an essentially normal intake of magnesium. This would seem to indicate a shift of magnesium from extracellular fluids into other body compartments.

Any such attempt to interpret changes in magnesium metabolism requires careful consideration of certain fundamental aspects of mineral and bone metabolism Recent studies have emphasized the need for revising our concept of the relationship between serum electrolytes and the mineral matrix of bone[31]. Such fundamental concepts as the Robinson phosphatase theory and the Albright-Reifenstein theory of parathormone action have been seriously questioned by this recent work[31]. Newer theories have been proposed which have direct bearing on speculations concerning magnesium metabolism. In the past studies of bone mineral have shown that the normal ratio of calcium to magnesium is 100 to 1[40]. Since these ratios are derived from bone ash it has been assumed that magnesium forms an integral part of the crystalline structure of bone. According to the newer concept of bone structure there is a tightly bound hydration shell of ions in contact with the bone crystal at the solute crystal interface in which mineral ions are held by electrostatic attractions[31]. Perhaps this is the locus of "bone magnesium" rather than the crystalline solid phase of bone. For practical considerations, at any rate, there is sufficient magnesium *in vivo* intimately associated with bone to constitute an important reservoir of this ion. Moreover, just as with the other electrolytes found in bone, this deposit of magnesium takes considerable priority in the body economy. Apparently the effect of bone is demanding rather than regulatory on the extracellular fluid concentration of the ions that comprise its structure. For example, it has been previously shown by Albright[1] that attempts to elevate serum calcium by supplementary calcium therapy following operation for hyperparathyroidism may be thwarted by bone absorption of calcium. This absorption continues until the skeletal deficits are satisfied. Likewise in their magnesium deficiency studies, Kruse's group[32] demonstrated that bone continues to accumulate magnesium as the animals grow despite deficient magnesium intake while the extracellular fluid concentration steadily declines.

Throughout these investigations in mineral and bone metabolism a curious antagonism between calcium and magnesium in the body has been noted despite some obvious similarities in the action of the 2 ions. This has been reviewed extensively[32]. Both low serum magnesium and low serum calcium increase neuromuscular irritability, while high concentrations of these ions have a converse effect on nervous functions[10]. On the other hand magnesium narcosis, produced experimentally by magnesium injections, is promptly antagonized by parenteral injections of calcium[28]. Furthermore

raising the percentage of calcium in the diet aggravates the physiological effects of a low magnesium diet[3]. Likewise calcium and magnesium antagonism can be observed in other respects. High dietary concentrations of either ion increases excretion of the other. Maintaining animals on diets deficient in either calcium or magnesium over some period of time results in alterations in bone structure whereby the relative concentration of the deficient ion falls while the concentration of the other ion in bone mineral rises.

It has been shown that parathormone influences magnesium metabolism as well as calcium metabolism. In experimental animals injections of parathormone cause a slight rise in serum magnesium[11]. This rise is transient, occurring within hours, and the magnesium level quickly returns to normal prior to the rise in serum calcium. It has been found likewise that parathormone causes increased urinary excretion of magnesium[34]. When parathormone was given to human subjects it caused a similar increase in urinary excretion of magnesium leading to negative magnesium balance during the period of observation[2,40]. This evidence forms the background for postulating the development of skeletal deficits of magnesium in hyperparathyroidism which would lead to deposition of magnesium after removal of the tumor.

While most of the body calcium is in the skeleton, much of the body magnesium is in muscle. Therefore a consideration of changes in the concentration of muscle magnesium is of paramount importance in any study of magnesium metabolism in human subjects. The work of Magnus-Levy[24] established the fact that the ratio of calcium to magnesium in muscle is only 1 to 3, a marked contrast to the situation in bone. However, present evidence indicates that this intramuscular magnesium is tightly bound and resistant to changes in extracellular fluid concentration. In the magnesium deficiency study in animals while skeletal deficits of magnesium occur there is only slight decrease in the concentration of magnesium in the soft tissues of the animals[5,41]. The suspension of muscle in magnesium-free parenteral fluid produces very little loss of muscle magnesium even after several days[4].

In the present patients we did not obtain values for the fecal excretion of magnesium and it could be argued that fecal loss could explain the decrease in extracellular magnesium. Other workers[2,40], however, have conducted complete balance studies including fecal magnesium excretion in patients with hyperparathyroidism during the preoperative and postoperative period, and found no great change in fecal magnesium excretion after operation. Instead they showed that true retention of magnesium occurred which must involve a shift of magnesium to intracellular compartments. They found hyperparathyroid patients who were in negative magnesium balance preoperatively who reverted to positive balance after operation primarily by a sharp reduction in urinary excretion of magnesium. At the time these studies were conducted there was little interest in the possible symptomatic effects of magnesium deficiency but their findings are quite pertinent. Tibbetts and Aub[40] studied one patient in great detail and attempted to ascertain the body compartments responsible for magnesium retention. Using the known facts about the ratio of calcium to magnesium in muscle and bone they compared the relative amount of calcium and magnesium retained in the postoperative period. By doing this they hoped to establish whether muscle or bone was the principal site of retention. In this well studied patient cal-

cium and magnesium were retained following operation in the ratio of 100 parts of calcium to 7 parts of magnesium. This ratio falls between the ratio of calcium to magnesium in muscle and bone. Therefore they felt that retention of magnesium by bone alone would not explain their observations and some retention of magnesium by muscle must also occur. This conclusion would seem at variance with the studies which showed that unlike bone magnesium, muscle magnesium is not freely available and labile. However, the experimental work on which the stability of muscle magnesium is based is concerned with transudation of magnesium through the membrane of intact muscle and does not include the possibility of frank destruction of soft tissue. Actual breakdown of muscle with negative nitrogen balance might occur in a disease like hyperparathyroidism which has marked systemic manifestations with increased catabolism. Conceivably, therefore, in hyperparathyroidism muscle deficits could occur which would absorb magnesium in the recovery period. On the other hand, it is known that in disease of bone the relative amounts of magnesium may be increased[27]. In osteomalacia there is such an increase in the concentration of magnesium in the diseased bone that the ratio of calcium to magnesium may be 100 to 7 which is as high as the ratio of retention of these ions observed in Tibbett's and Aub's case[27]. A similar situation might exist in the bone which is rapidly formed in the repair period after the removal of a parathyroid adenoma, so that bone absorption could still be the principal mechanism of retention. Analysis of bone and muscle biopsy specimens obtained in the pre- and postoperative period would probably decide the issue. Such studies have not yet been reported to our knowledge.

Although the number of cases of hyperparathyroidism in which magnesium metabolism has been studied are limited, it has been noted that retention of magnesium does not occur in all cases. At least clinically it would seem that the existence of skeletal demineralization is the best indication as to whether magnesium retention will occur. In the cases of Tibbetts and Aub marked postoperative retention of magnesium was noted in the patient who had generalized bone disease by roentgenographic examination while there was little postoperative change in the second patient in whom generalized decalcification was absent. We have obtained magnesium studies on a patient with proven hyperparathyroidism in whom there was no bone disease demonstrable on Roentgen-ray examination. In contrast with the marked retention of magnesium in association with severe demineralization of bone which we observed in patients, I.C. and R.C., the patient without bone disease showed only a mild decline in urinary excretion of magnesium and no change in serum magnesium. Likewise postoperative hypocalcemia did not occur and her clinical course was uncomplicated.

To test the hypothesis that symptomatic magnesium deficiency occurs in the recovery period of hyperparathyroidism it is necessary to demonstrate that symptoms occur at the time of magnesium deficiency in this disease when more conventional causes of tetany can be excluded. Likewise it should be possible to obtain a therapeutic response to magnesium administration. In the case of patient, I.C., the profound and prolonged drop in urinary excretion of magnesium was accompanied by a subsequent drop in serum magnesium. At this point in the patient's clinical course, symptoms resembling tetany occurred while there

was no hypocalcemia or alkalosis to explain her symptoms on conventional grounds. Patient, R.C., demonstrated a similar pattern of postoperative magnesium metabolism. It is curious to note the similarity between the symptoms in this patient and the toxic psychosis noted in the magnesium deficiency cases reported by Flink *et al.*[9]. Her acute episode of mental disturbance occurred during the period of postoperative hypomagnesemia. It is possible that there was some relation between the magnesium deficiency and the mental changes, although the origin of the mental disturbances may well have been primarily in the emotional background of the patient. In neither case was there a prompt response to parenteral magnesium therapy. This was disappointing but we do not feel that this fact seriously detracts from the thesis that magnesium deficiency is responsible for the neurologic symptoms. There are several reasons for this viewpoint. The underlying physiological mechanisms by which magnesium deficiency mediates neurologic symptoms is apparently more complex than a simple state of hypomagnesemia. We believe that this complexity explains the lack of prompt response to magnesium therapy. There are analogies with other symptomatic electrolyte disturbances. The fact that calcium and potassium deficiences cause profound physiological disturbances in patients is well accepted. Yet Elkinton and Danowski[8] pointed out that the muscle paralysis and paralytic ileus associated with potassium deficiency "are not invariably concomitants of low potassium levels in plasma and hence serve to emphasize the incompleteness of our knowledge." Despite this fact the actual occurrence of symptomatic total body depletion of potassium is now a well recognized clinical entity requiring vigorous treatment. Even with hypocalcemic tetany it is not always possible to correlate serum levels of the ions at any one point with the status of neuromuscular irritability at that time. Experimentally, for example, dogs with latent tetany after thyroparathyroidectomy may have serum calcium levels as low as those that occur in acute hypocalcemic tetany yet have no symptoms of tetany[26]. It is not too surprising therefore that there is a similar uncertainty about which parameter of magnesium is significant in the mediation of symptoms in magnesium deficiency.

The theoretical considerations of the Loeb equation would lead one to suppose that extracellular magnesium is the significant variable and there is abundant evidence from the animal work and clinical observations to support this motion. In the original studies with magnesium-deficient diets Kruse's group[19] demonstrated that the onset of neurologic changes in the animals was correlated with the development of low levels of serum magnesium, particularly the ionized magnesium fraction. Most of the clinical reports of symptomatic magnesium deficiency have stressed the importance of hypomagnesemia in the production of tetany. Still further support for the extracellular locus of magnesium activity is derived from considering the effects of high serum magnesium. Magnesium has been used for some time in pharmacological doses as an anticonvulsant in eclampsia and other conditions. High serum levels of magnesium produce complete flaccidity of muscles, respiratory paralysis, and coma[28]. These effects have been shown to be due primarily to peripheral action. Magnesium exerts a neuromuscular block by a mechanism somewhat similar to that of curare. It reduces the end plate potential by decreasing the amount of transmitter (acetyl-

choline) released at the neuromuscular junction[6]. Calcium promptly and dramatically relieves these symptoms of magnesium narcosis[28]. The speed of the process suggests an extracellular reaction. It seems logical, therefore, that magnesium deficiency which augments neuromuscular irritability would operate by a reduction in the extracellular concentration of magnesium.

Just as with the neuromuscular effects of low potassium and low calcium there are many inconsistencies in experimental and clinical observations which conflict with the view that low serum levels of magnesium are the sole cause of symptoms. In their experiments with magnesium deficient rats Greenberg and Tufts[41] noted discrepancies between the degree of hypomagnesemia and the development of tetany. Serum magnesium values fell to lowest levels shortly after the low magnesium diets were started. By the time that symptoms of hyper-excitability developed, serum magnesium values had risen and were only slightly subnormal. (However, these measurements were on total and not ionizable magnesium.) Even more significant was their finding that intraperitoneal injection of magnesium failed to prevent convulsions for 4 to 5 hours after administration. They concluded that this finding "does not harmonize with a view that the hyperirritability in this condition is a peripheral affectation or is merely the result of an ion imbalance in the body fluids"[41]. However, determinations of the concentration of magnesium in the brain and soft tissues of animals sacrificed at the time of convulsions have revealed only slight reductions from the normal levels of magnesium in these tissues[5,41], which argues against postulating disturbed enzyme functions or other intracellular effects as the mediation of neurologic changes at least in the experimental work. Furthermore although interest has centered on the role of hypomagnesemia in symptom production in patients there are disturbing inconsistencies with the theory of purely extracellular magnesium effects even in the clinical observations. Hypomagnesemia has been noted in some patients without symptoms, as in the cases reported by Martin, Mehl and Wertman[25] and symptomatic patients have improved without return of serum magnesium to normal levels. Likewise therapeutic responses to parenteral magnesium have been too slow and variable to permit acceptance of the view that magnesium deficiency is solely an extracellular phenomenon.

One further fact is worthy of note in attempting to establish the mechanism of symptom production in magnesium deficiency. Soffer's group[37,38] has shown that marked alterations in the ionized fraction of serum magnesium can occur. In hyperthyroidism the percentage of bound magnesium increases from a normal range of 3% to 22% to levels between 21% and 60% early in the disease. In myxedema all of the serum magnesium may be ionizable. In hyperthyroidism, patients with the disease present for more than 2 years show a return of the ionizable fraction of serum magnesium to normal levels. Possibly alteration in the ionized fraction of magnesium with changes in serum protein binding capacity can explain the discrepancies between the degree of total hypomagnesemia and the neurologic symptoms in some of the reported cases. There is no present evidence that such changes occur, however, in hyperparathyroidism or the other magnesium-deficiency cases that have been studied.

Thus we are left with a presently confusing view of the primary effective locus of magnesium deficiency. The experimental work with pure mag-

nesium deficiency in animals is only crudely analogous to the clinical situations. The important difference between the 2 situations is that the disease states so far studied, including hyperparathyroidism, show marked systemic manifestations. In these diseases there exists a good possibility that breakdown of muscle may increase the importance of soft tissue deficits of magnesium in the anabolic phase after operation.

It is uncertain then whether extracellular or intracellular deficits of magnesium, sudden changes in the ratio of these values, or changes in the ionized fraction in the serum are the important variable in magnesium deficiency. We believe that in hyperparathyroidism, a condition of over-all magnesium deficiency is present in response to the chronically elevated levels of parathormone. Following operative removal of the adenoma, there is a sudden retention of magnesium by bone or soft tissue, or both. This imposes a sudden decrease in extracellular magnesium concentration reflected in decreased urinary excretion and a drop in the concentration of serum magnesium. Perhaps more importantly this retention produces derangements in the ratio of intracellular and extracellular magnesium. At any rate symptoms of magnesium deficiency appear when this sudden change in magnesium metabolism occurs.

From the clinical viewpoint, the reason for considering the exact mechanism of the effects of magnesium deficiency in such detail is the role that such information has in interpreting therapeutic responses. If intracellular deficits are a significant factor in producing symptoms then the adequacy of magnesium therapy is an important consideration. It has been estimated that 1 gm. of $MgSO_4 \cdot 7H_2O$ contains 99 mg. of magnesium. Since there is a total of some 20 gm. of magnesium in the body, significant depletions of magnesium will not be corrected by giving a few grams of $MgSO_4$. Only a small percentage of administered oral magnesium is absorbed. The parenteral route of administration is necessary for effective therapy[33]. Ten to 20 gm. of $MgSO_4$ per day intramuscularly in divided doses can be given as long as urinary output is adequate. Such heavy doses may well be necessary to correct total body deficiency of magnesium and failure to have given adequate amounts may well explain the variations in clinical responses to magnesium therapy in some of those patients suspected of having symptomatic magnesium deficiency.

It is not necessary to postulate that magnesium deficiency occurs as an isolated phenomenon or is the sole cause of neurologic symptoms in clinical situations. The need for considering the multiplicity of electrolyte abnormalities is now axiomatic.

The gravity of symptoms in the diseases in which magnesium deficiency is reported to occur makes attention to a contributing role of magnesium imperative and requires further investigation.

Summary. 1. Carefully controlled studies in animals have conclusively demonstrated that magnesium deficiency leads to profound neurologic changes including tetany. This is correctable by the restoration of magnesium to the diet or by parenteral injections of magnesium, but the improvement is gradual.

2. Clinical reports have appeared indicting magnesium deficiency in various disease states as the cause of tetany and other neurologic symptoms under circumstances where these symptoms could not reasonably be attributed to more conventional causes. In general,

improvement with magnesium therapy was noted in these cases, but this effect was not invariable or prompt.

3. The parathyroid gland influences magnesium metabolism. Experimentally in animals and in humans parathormone increases urinary excretion of magnesium. Hyperparathyroid patients have been studied who were in negative magnesium balance before operation and reverted to positive balance postoperatively.

4. One patient with hyperparathyroidism displayed symptoms of tetany while a second developed a period of disturbed psychomotor activity following removal of the parathyroid adenoma. At the time these symptoms developed there was a marked urinary retention of magnesium and a drop in serum magnesium levels, resulting from a shift of magnesium to intracellular compartments. More conventional causes of the neurologic disturbances were excluded and it is believed the altered magnesium metabolism was the cause of the tetany and may have contributed to the psychomotor disturbance.

Few generalizations can be made from the limited clinical observations so far made on patients with hyperparathyroidism. It seems, however, that the existence of bony demineralization predisposes to postoperative retention of magnesium. At present it is uncertain which parameter of magnesium concentration is effective in mediating the symptoms of magnesium deficiency, but the possible importance of intracellular deficits may well explain the variable results with magnesium therapy since the doses of magnesium employed have often been very small in comparison with the size of the intracellular reservoir of magnesium which may be depleted.

5. Further careful study is indicated to establish the exact role of magnesium deficits in the symptoms of postoperative hyperparathyroid tetany and other diseases in which disturbances of magnesium metabolism occur.

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OPHTHALMOLOGY

UNDER THE CHARGE OF

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THE OCULAR LESIONS OF PULSELESS DISEASE

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IN 1952, Caccamise and Whitman[10] published what they thought to be the first report of a case of so-called pulseless disease to appear in the American literature. They stated that this was "apparently the first case to be reported outside of Japan." However, in 1954, Caccamise and Okuda[9], in a subsequent report of the same case, amended these statements by saying that, though this case was the only one in the non-Japanese literature reported specifically as pulseless disease, "Aggeler, Lucia and Thompson[1] described a case which undoubtedly is an example of this condition. In their report mention is made of 5 additional cases from the literature that might be included in this group. A review of American ophthalmic literature failed to reveal any mention of Takayasu's or pulseless disease." In "pulseless disease," the pulses are absent or undetectable characteristically only in the upper part of the body. And, as noted by Pinkham[44], obliteration of the branches of the aortic arch with consequent absence of radial and carotid pulses has been noted and recorded in a number of cases in the past one hundred years.

In addition to the general term, aortic arch syndrome, and the designations, "pulseless disease" and "Takayasu's disease," various names have been proposed for this condition, for example, thromboangiitis obliterans subclavio-carotica, carotid-subclavian arteritis, obliterating arteritis of supra-aortic trunks in young women, Myaku-Nashi disease, arteritis epiaortica, reversed coarctation of the aorta and reversed isthmus stenosis syndrome. The last two terms suggest that the absence of pulses is on the basis of a congenital anomaly. Thus, Dry[15], in discussing Giffin's[20] case report, stated: "An acquired obliterative process, which would involve the main arteries arising from the aortic arch selectively, would explain the physical findings described in this case; but it is hard to conceive of an acquired process which could display such selectivity. It is true that extensive syphilitic aneurysm involving the aortic arch such as has been reported by several authors is capable of producing an obliteration of the blood supply to the upper extremity, head and neck, but in this instance, serologic, clinical and roentgenologic studies definitely rule out this condition. It seems more than likely that the interference of the circulation to the head, neck and upper extremities of this patient is dependent on a congenital anomaly of the

great vessels or at least that the ground work has been set by such an anomaly." Ross and McKusick[46] noted that the less common patterns of aortic arch branching were encountered at necropsy with unexpected frequency in cases of the aortic arch syndrome. But they expressed the opinion that, though this was a possible contributing factor, it was not a primary cause of the syndrome. And Lewis and Stokes[29] stated that, "The congenital anomalies of arteries are not suppressions of arterial supply, they are merely unusual arrangements of supply." In reference to their own case, they said that the findings in their patient were evidence of "a gross defect of circulation to the head and limbs. To account for this state an anomaly of development would be, by itself, an inadequate explanation. It would seem necessary to adopt an explanation embracing an acquired lesion. The nature of this acquired lesion remains obscure." Such terms as "reversed coarctation of the aorta" and "reversed isthmus stenosis syndrome" would seem, then, to be unacceptable substitutes for "pulseless disease."

ETIOLOGIC TYPES OF THE AORTIC ARCH SYNDROME. Ross and McKusick[46] included as instances of the aortic arch syndrome only those cases in which the obstruction was located at or near the origin of the great vessels from the aortic arch. They reviewed the reports of 100 cases and classified the cases into 12 groups, according to their presumed etiology. The lesions said to be responsible for the production of the syndrome were: (1) obscure; (2) syphilitic aortitis with aneurysm; (3) syphilitic aortitis without aneurysm; (4) atheromatosis; (5) trauma with aneurysm; (6) trauma without aneurysm; (7) congenital anomalies; (8) chronic dissection of the aorta; (9) thrombophilia; (10) nonsyphilitic aortitis, the "young female" group; (11) embolism; and (12) extravascular upper mediastinal tumor.

As suggested by Ross and McKusick[46], the name, "Takayasu's disease," should be used to designate only those special instances of the aortic arch syndrome which occur in young women and which are caused presumably by nonspecific arteritis. "Takayasu's disease" seems to be used synonymously with "pulseless disease" and yet, as a matter of fact, there seems to be some question whether Takayasu[52] noted the absence of pulses in his first case. Caccamise and Okuda[9] wrote: "In 1908, Takayasu[52] reported a peculiar case with cataracta complicata and unusual ocular fundus findings. At the same meeting Onishi[41] and Kagoshima[25] reported 2 similar cases with the added observation of absent radial pulses in one of the patients." It would appear from Pinkham's[44] table that Takayasu[53] and Onishi[42] both noted the absence of radial pulses but that absence of pulsations in the common carotid arteries was recorded definitely for the first times in 1939 by Yasuda[57] and by Dodo[14]. There was some question of its having been noted by several authors before that time, starting with Nakashima[39] in 1921.

As the disease processes responsible for occlusion of the arteries arising from the aortic arch are progressive in nature, it seems logical to suppose that cases may be encountered before the syndrome is complete. Ross and McKusick[46] noted the occurrence of incomplete syndromes especially in cases of atheromatosis of the aortic arch and of syphilitic aortitis without aneurysm. Cases of incomplete pulseless disease have been reported also by Kirklin[26], by Ask-Upmark[5], by Barker and Edwards[6], by Van Buchem[8], and by Gottsegen and Szam[21]. In Van Buchem's[8] case, biopsy of a branch of a subclavian artery showed a stenos-

ing panarteritis. McLean[33] thinks that a difference in the blood pressure in the two arms may be the earliest sign of the disease. In the main, however, symptoms will not bring the patient to the physician until one common carotid is obliterated and the other considerably involved. And involvement of the subclavians seems to precede demonstrable involvement of the carotids. The absence of one radial pulse, which is probably the earliest definite sign of the disease, is often discovered accidentally or incidentally but the diagnosis is not established usually until at least three of the main arteries to the upper part of the body are occluded.

GENERAL SYMPTOMATOLOGY. Ross and McKusick[16] stated: "The clinical manifestations result almost exclusively from the impediment to carotid artery blood flow (interference with vertebral blood flow by obstruction of the subclavian arteries is doubtless an additional factor of importance in some cases). Whereas cerebral, eye, ear and face changes are outstanding features of the clinical picture in some cases, symptoms referable to the arms are conspicuous by their absence." Caccamise and Whitman[10] stated that the outstanding presenting symptoms of pulseless disease are visual disturbances and syncopal attacks frequently associated with convulsions. Caccamise and Okuda[9] stated: "In addition to the radial pulse and blood pressure abnormalities, the following nonocular findings have been noted: delicate skin, fine poorly pigmented hair, clubbed fingers (unusual), attacks of syncope attributed to hypersensitivity of the carotid sinus, intermittent claudication in the upper extremities, episodes of speech disturbance, attacks of pain in the orbit, eyeball and chest, hemiplegia, hypo- and amenorrhea, perforated nasal septum (frequent), hearing defects, and increased sedimentation rate." Hsioh-Teh, An and Fu-Hsi[24] classified the manifestations of pulseless disease into: (1) Local ischemic symptoms: intermittent claudication of the arms and jaws, emotional instability, impaired memory, transient epileptiform seizures or attacks of hemiplegia, local tissue atrophy of the face and facial bones, spontaneous perforation of the nasal septum, ulceration of the palate or of the concha of the external ear and visual disturbances; (2) Signs of collateral circulation; (3) Carotid sinus syncope; (4) Cardiovascular symptoms: arterial hypertension in the lower extremities, sinus tachycardia, and, later, left ventricular hypertrophy and failure; and (5) Fever, leukocytosis and increased sedimentation rate.

Currier, De Jong and Bole[13] reviewed 40 cases reported in the literature and listed the most common symptoms as follows: visual disturbances in 32 cases, syncope and loss of consciousness in 29, dizziness and vertigo in 19, headache in 17, paralysis in 15, sensory changes in 10, convulsions in 9, carotid sensitivity in 9, aphasia in 8 and bulbar signs in 5. These authors noted that some authors had reported a high incidence of hypertension in the lower extremities. However, Currier, De Jong and Bole[13] found that the blood pressure in the legs was normal in the majority of the cases in which it was recorded; it was subnormal in their own case, which was apparently, however, one of syphilitic arteritis. They noted also that pneumoencephalograms, when done, showed unilateral or bilateral cortical atrophy with dilatation of the lateral ventricles and that electroencephalograms, when done, were nonspecific in character and did not show any definite focus.

Ross and McKusick[16] called attention to the fact that, in the aortic arch

syndrome, characteristically, the pulses in the arm become impalpable before the blood pressure is completely unobtainable even by the usual methods. If the local blood pressure beyond an obstruction is measured by intraarterial techniques, they said, it will be found that there is a great reduction in pulse pressure but often only a slight reduction in mean arterial pressure. The paucity of clinical evidence of ischemia of the arms may be a reflection, they suggested, of the distinction between absence of pulses and absence or serious reduction of blood flow; in the case of obstruction at the aortic arch, the normal pressure oscillations are damped but a steady mean arterial pressure is maintained. Ross and McKusick[46] also outlined a method for estimating the blood pressure in the arm when it is not obtainable by auscultation: the cuff is inflated with the arm raised above the head, the arm is lowered and the pressure is released slowly; the pressure reading at the time the first flush appears in the hand and forearm is approximately the mean arterial pressure.

OCULAR SYMPTOMS AND SIGNS. The chief ocular symptom is that of recurrent episodes of transient loss of vision followed in many cases by permanent loss, at times of sudden onset and at other times gradually progressive in development, even to the point of total blindness in some instances. The episodes of transient blurring of vision are usually of short duration, a few seconds to a few minutes, and are brought on characteristically by change of posture from the reclining to the upright position or by raising the head. Vision returns promptly when the head is lowered or when the individual lies down. The most characteristic objective ocular signs are said to be the progressive formation of peripapillary arteriovenous anastomoses and cataracts.

The patient who was the subject of the original report by Caccamise and Whitman[10] had characteristic symptoms and signs of pulseless disease. She was 19 years old at the time of her examination and had commenced to have fleeting episodes of syncope and loss of vision 2½ years previously. Permanent loss of vision had developed in the right eye rapidly in one day and in the left eye gradually over a period of 6 months. A cataract had been extracted from the left eye 6 months previously. No pulse could be obtained in either radial, ulnar or temporal arteries or in the right common carotid, and only a faint pulse in the left carotid. Vision of the right eye was limited to light perception and light projection was poor; a mature cataract prevented a view of the fundus. Vision of the left eye was reduced to ability to see hand movements at 2 feet; the eye was aphakic. Caccamise and Okuda[9] later presented a diagram and gave a detailed description of the ophthalmoscopic appearance of the fundus of this eye. They wrote: "The conversion of the entire retinal vascular tree into simple peripapillary arteriovenous loop anastomoses is evidence of the far-advanced stage of the disease in this patient. There was no discernible difference in the appearance of the venous and arterial components of the loops. The disc was yellowish-white with fairly distinct edges. There was no apparent cupping. The papillary arteries and veins extended out from the disc onto the retina for a distance of one to two disc diameters. There each artery was seen to form a terminal loop anastomosis with the accompanying vein. This was visible inferiorly, nasally, and superiorly. There was no continuation of the retinal vessels beyond these loops. The choroidal vessels were only

faintly visible peripherally through the retina. No hemorrhages or exudates were seen. The macula was clear without a foveolar reflex."

Pinkham's[44] patient was seen apparently at an earlier stage of the disease; but her initial symptoms had been sudden loss of vision of the left eye and difficulty in speaking and swallowing 11 months previously. She had developed a left hemiparesis 6 months before the time of her examination. The radial and carotid pulses were absent. Vision of the right eye was 20/25, but the vision of the left eye was reduced to light perception only. Ophthalmoscopic examination revealed optic atrophy and macular degenerative changes in the left eye and fragmentation of the blood stream in the retinal vessels of both eyes. The retinal arterial pressure was low (dynamometer readings 25/20). Fragmentation and slowing of the blood stream could be observed in the conjunctival vessels with the slit lamp.

Lowered retinal arterial pressure is probably the earliest objective ocular sign of the disease, as suggested by Pinkham, and visible fragmentation of the blood stream in the retinal vessels is probably an early sign also. Ischemic patches in the retina were associated with these two signs in the only case of pulseless disease I have seen personally, the case reported by Giffin[20].

It is undoubtedly true that the signs and symptoms presented by any given case of pulseless disease at a single examination will depend on the stage of the disease at the time of the examination. However, it is of some interest to note the percentage occurrence of some of the more prominent manifestations of the disease. Pinkham[44] analyzed the ocular symptomatology of 87 cases, 50 of which had been reported by Japanese authors. He found that transitory disturbance in vision had been recorded in 70% of the cases, cataract in 45%, arteriovenous anastomoses in 39%, iris atrophy in 38%, retinal hemorrhages in 38%, retinal microaneurysms in 33%, dilated retinal vessels in 23% and lowered retinal arterial pressure in 7%. Analyzing the findings in an additional group of 40 cases which I was able to collect from the literature and adding them to Pinkham's[44] figures did not alter these percentages materially except perhaps those for transitory disturbance in vision and for lowered retinal arterial pressure. The percentage occurrence in the total group of 127 cases of the previously tabulated lesions was 58, 41, 39, 33, 36, 32, 28 and 14 respectively. Ross and McKusick[46] analyzed the recorded findings in 40 selected cases. All four main arteries were involved in 29 of these cases and at least two arteries, one a common carotid, in the other 11. The percentage occurrence of the lesions was in the main somewhat lower in this group of cases. Transient disturbance in vision was noted in 43%, cataract in 30%, iris atrophy in 18%, retinal microaneurysms in 8% and progressive development of arteriovenous anastomoses frequently (number of cases not given for this last finding). Apparently only a few cases of the "young female" type were included in this group. To determine whether the ocular lesions presumed to be characteristic of pulseless disease occur more frequently in this "young female" group than in the group of aortic arch syndromes as a whole, the findings were analyzed in the 73 of the 127 patients who were women less than 40 years of age. It was found that, with the exception of transient disturbances of vision, ocular lesions were more frequent in the "young female" group than in the group including all types of aortic arch syndromes and, with the added exception of lowered

retinal arterial pressure, much more frequent than in the group of syphilitic aneurysms of the aorta. The comparative figures for the "young female" group (presumably nonspecific arteritis) and for the syphilitic aortic aneurysm group are: transitory disturbance in vision, 63% and 50%; cataract, 55% and 9%; arteriovenous anastomoses, 48% and 0; iris atrophy, 47% and 0; retinal hemorrhage, 49% and 0; retinal microaneurysms, 37% and 0; dilated retinal veins, 29% and 17%; low retinal arterial pressure, 11% and 8%; fragmented blood stream, 12% and 0; rubeosis iridis, 4% and 0; peripheral anterior synechiae, 3% and 0; optic atrophy, 8% and 0; and permanent loss of vision, 24% and 17%.

If note had been taken of the retinal arterial pressure in all cases, it is probable that it would have been found to be low in a much higher percentage of cases as transitory disturbances of vision of amaurosis fugax type and relatively low retinal arterial pressure seem to be earmarks of any type of obstruction to the circulation through the internal carotid artery. Episodes of amaurosis fugax had occurred in 15 of 39 cases of unilateral occlusive disease of the carotid artery studied by Hollenhorst[23]. And in all 7 cases of intermittent insufficiency of the internal carotid arterial system studied by Millikan, Siekert and Shick[36], the retinal arterial pressure was found to be lower in the eye on the affected side than in the fellow eye. However, to the best of my knowledge, progressive formation of peripapillary arteriovenous anastomoses, atrophy of the iris and the rapid development of complicated cataract, which are the most characteristic ocular lesions of pulseless disease, have not been reported in cases of unilateral atherosclerosis or thrombosis of the internal carotid artery. This may be because of the more efficient collateral circulation in the latter type of case. In pulseless disease, the brain and presumably the eyes, must depend for nutrition on the rather inefficient collateral circulation which, according to Currier, De Jong and Bole[13], is developed from the aorta through the intercostal arteries to the internal mammaries and then through the subclavian arteries to the vertebrals and thus eventually to the circle of Willis.

There is a definite postural element in the low retinal arterial pressure and in the visible fragmentation of the blood stream in the retinal vessels, as well as in variations of visual acuity. Shimizu and Sano[49] noted that in one of their patients vision was 0.1 with the face tilted 45 degrees upward, 0.7 with the face straight forward and 0.9 with the face tilted 45 degrees downward; these alterations in visual acuity could be shown by ophthalmoscopic observation to be correlated with the amount of blood circulating in the retinal vessels. In the patient studied by Kouretas and Djacos[27], when standing or sitting, the disk was slightly pale, the arteries were narrow, the veins were irregular in caliber and the blood stream in them was fragmented, and there were numerous miliary aneurysms in the retina. When the patient was lying down, the disk was better colored, the veins were larger and the blood stream was not fragmented. And, when the patient was placed in the Trendelenburg position, the arteries were normal, the veins engorged and the miliary aneurysms were barely visible. In the sitting position, the retinal arterial pressure was less than 10 mm. Hg and the central retinal artery and its branches disappeared from both retinas when pressure was made on one globe. This latter effect was less readily obtained when the patient was lying down, in the Trendelenburg position especially. It is of interest that Savory[47], who reported

in 1856 a case which today would be diagnosed as pulseless disease, called attention to the effect of posture on the vision of his patient, a woman 22 years of age. He wrote: "The vision of both eyes is very weak and imperfect, but it is decidedly much better when she lies down; in this position she can see the length of the ward, but when sitting up she can scarcely see at all."

THE COURSE OF PULSELESS DISEASE AND OF ITS OCULAR LESIONS. Hsioh-Teh, An and Fu-Hsi[24] stated that the duration of pulseless disease might vary between 1½ and 14 years or more; it was more than 15 years in Mangold and Roth's[30] patient. Currier, De Jong and Bole[13] said that the disease usually affects first one and then the other common carotid artery allowing time for collateral circulation to form. If it is to be fatal, death usually occurs in less than 3 years for after this the collaterals take over. However, Frövig and Löken's[19] patient died 5½ years and Savory's[47] 6 years after the first symptoms appeared.

The general or average course of development of the characteristic ocular lesions was outlined by Shimizu and Sano[49]. Stating that visual disturbances usually are the reason for the patient's consulting the physician, they wrote: "First there is noticed streaky congestion of the conjunctiva. Then, one after another, the following symptoms appear: flashes of light, field defects and blurring especially on turning the head upward. . . . Later, cataracts develop and the patients become totally blind; this state is reached from 2 to 4 years after the onset of visual symptoms. . . . Before cataracts develop, examination of the optic fundus discloses interesting changes. In the early stages (Fig. 2*a*) the fundus is practically normal with but a few arteriovenous anastomoses in the periphery. But soon they become thinner, and rosary-like swellings along the veins are seen. Vascular anastomoses surround the papilla like a wreath (Fig. 2*b*). In the third stage this wreath covers the papilla which appears atrophic and anemic. The peripheral part of the retina atrophies and only a few spurs of vessels are visible. Finally the lens becomes turbid and cataracts develop."

The time required for the development of the various ocular lesions seems to vary considerably in different cases. Thus punctate hemorrhages and microaneurysms were present in the retina in Friede's[18] case 4 months after onset, while in one case reported by Skipper and Flint[50] only a few were present 3½ years after the first symptoms of intermittent blurring of vision. And in Lewis and Stokes'[29] patient, the fundi were normal 7 years after the discovery of absent radial pulses, except for the presence of primary optic atrophy in the right eye. Peripapillary arteriovenous anastomoses had developed within a 2-year period in Shimizu and Sano's[49] patient and within 2½ years after onset in the case reported by Caccamise and Whitman[10] and Caccamise and Okuda[9]. On the other hand, in a patient who had had transient obscurations of vision in the right eye for 10 years, Ask-Upmark[5] found fragmented blood stream, microaneurysms and hemorrhages in the retina but he did not observe arteriovenous anastomoses and cataracts until 4 years later.

Friede[18] noted new formed vessels in the right iris of his patient 4 months after the development of the first symptoms and microaneurysms and hemorrhages in the retina. Fourteen months later, the microaneurysms and hemorrhages were still present in both retinas and there was vascularization of both irides; in addition, the right

iris was atrophic with peripheral anterior synechiae, the cornea was cloudy and the lens was swollen and cloudy. In the case reported by Harbitz[22] and by Raeder[45] atrophy of the right iris was noted at the first examination 1½ years after the onset and vascularization of the iris one month later. In this case, sudden blindness with the ophthalmoscopic picture of closure of the central artery of the retina occurred 16 months after the onset of the disease while sudden blindness with the late ophthalmoscopic picture of simple optic atrophy was the initial symptom of the disease in Pinkham's[44] patient.

In the case reported by Elliot, Ussher and Stone[17], cataracts developed rapidly in both eyes 19 months after the onset of the disease. Skipper and Flint[50] stated that cataracts usually developed within 12 to 18 months after the onset of the first symptoms, but that, in one of their cases, cataracts did not develop until 13 years after the onset.

HISTOLOGIC LESIONS IN THE ARTERIES AND EYES. Necropsies have been performed on a number of patients with occlusions of the branches of the aortic arch. Syphilitic arteritis with aneurysm has been found in some cases, for instance in Parsons'[43] patient. Cohen and Davie[11] reported a case of aortic aneurysm in which it appeared that syphilitic endarteritis obliterans had been superimposed on atheromatous plaques. Extensive atheroma of the arch of the aorta was found by Sen Gupta and Ghosh[48]in their case. Shimizu and Sano[49] stated that Ohta[40] published the first necropsy report on a case of pulseless disease in the "young female" group; he found thrombi in the subclavian and common carotid arteries due to periarteritis of unknown origin. It is of interest to note in this connection that Savory[47] reported in 1856 the findings at necropsy in a young woman of 22 who died 13 months after admission. All the main arteries of both upper extremities and of the left side of the neck were reduced to solid cords with organized thrombi. The right common carotid was contracted and its walls were much thickened. Savory[47] said: "The condition in which the arteries were found after death, the morbid changes which they had undergone, will generally, I imagine, be regarded as the result of inflammation of their walls." This was interpreted as arteritis of unknown origin though the question of syphilis was raised.

Harbitz[22] and Raeder[45] and Shimizu and Sano[49] found thrombi in the subclavian and common carotid arteries of their cases. Shimizu and Sano[49] thought that the thrombi were secondary to a panarteritis which had the histologic characteristics of tuberculosis but in which tubercle bacilli could not be demonstrated. Myers[38] and his coworkers interpreted the lesions in their case as representing an arteritis which was accelerating the development of severe arteriosclerotic occlusive disease. Marinesco and Kreindler[31] thought that the obliteration of the common carotid arteries in their case was due probably to thromboangiitis obliterans. Maspetiol and Taptas[32] found it difficult to differentiate the arteritis present in their case from the lesions of thromboangiitis obliterans, periarteritis nodosa and temporal arteritis. Frövig and Löken[19] and Colon Rivera[12] thought that the arteritis present in their cases was of allergic-hyperergic origin. In Colon Rivera's[12] patient, a girl of 5, there was also evidence of generalized periarteritis nodosa.

Harbitz[22] and Raeder[45] described the microscopic changes present in the right eye of their patient, which was removed at necropsy one month after it had gone blind suddenly with the ophthalmoscopic picture of closure of

the central artery of the retina. There was severe atrophy of the anterior stroma of the iris with adhesions of the root of the iris to the posterior surface of the cornea and atrophy of the ciliary processes and muscle. There were far advanced cataractous changes in the lens. In the retina there were many old and recent hemorrhages in the nerve fiber, the ganglion cell and the inner nuclear layers in the neighborhood of the veins, some of which were much dilated. There were no lesions in the walls of the smaller retinal arteries; they were collapsed with folded internal elastic laminas. The central retinal artery did not show any signs of inflammation, degeneration, necrosis, embolism or thrombosis. The papilla was not excavated.

Frövig and Löken's[19] patient had had originally scattered small hemorrhages in the retina and some exudates thought to be due to arterial spasm. Later cataracts developed and both eyes were virtually blind at the time of death. Sections of the optic nerves showed an increased amount of fibrous tissue between the nerve fibers, more pronounced in the right where the myelin had completely disappeared. In the left nerve, only a few peripheral nerve bundles were demyelinated. There were no axis cylinders visible in the right nerve. Both central retinal arteries showed rather extensive fibrous thickening of the intima. Sections of the posterior parts of the retinas showed a reduced number of ganglion cells and degeneration of the remaining ones. The granular cells were reduced in number, especially in the internal layers, more so in the right retina. The vessels in the nerve fiber layer of the right retina were more or less obliterated.

A woman aged 19 observed by Trias de Bes, Sanchez Lucas and Ballesta Barcons[54] had clinically an atrophic iris with adhesions in the angle of the anterior chamber, a mature cataract and malignant glaucoma in the right eye and an arteriovenous anastomosis in the left retina. The right eye was enucleated. Microscopic examination showed a vascular connective tissue lamina of embryonic aspect extending in front of the retina as a pre-retinal membrane with its greatest thickness at the edge of the papilla and thinning out to a sharp edge in the equatorial region. A sort of truncated cone, not centered on the papilla, extended out from the papilla into the vitreous. It was formed by very delicate fibrous connective tissue containing blood vessels, either dilated capillaries or larger vessels with very fine walls. The retina was disorganized and there was gliosis and rich vascularization of the nerve fiber layer with vessels of large caliber. The authors raised the question whether these findings represented congenital abnormalities or were connected pathogenetically with the pulseless disease. In view of the presence of arteriovenous anastomoses in the other eye, it would seem probable that a similar process had resulted in the histologic picture of proliferative retinopathy in the enucleated eye.

MECHANISM OF PRODUCTION OF THE CHARACTERISTIC OCULAR LESIONS OF PULSELESS DISEASE. Shimizu and Sano[49] stated: "The visual symptoms are caused by occlusion of the carotid artery at the bifurcation. The external carotid gets sufficient blood from the subclavian artery via the arteria thyroidea inferior-thyroid gland-arteria thyroidea superior-arteria carotis externa, thus the circulation of the face and scalp is little disturbed. But the internal carotid artery lacks such anastomoses. The only way for the brain to get a blood supply of any importance is through the vertebral arteries–circle of Willis–middle and anterior

cerebrals. This route is inadequate to supply the ophthalmic arteries sufficiently and thus chronic increasingly severe circulatory insufficiency of the eye results."

According to Pinkham[44], "Sudden loss of vision is probably due to temporary marked reduction in central retinal arterial flow approximating occlusion of the artery. Primary optic atrophy may follow. Sometimes there is gradual diminution in vision without cataract formation due no doubt to the gradual atrophy of the retinal elements. Again these findings are compatible with the chronic subnutrition to the eye." Raeder[45] thought that the ophthalmoscopic picture of closure of the central retinal artery seen in some cases of sudden loss of vision could be attributed to sudden collapse of the artery due to a severe drop in blood pressure.

As noted by Caccamise and Whitman[10] and by Shimizu and Sano[49] cataract formation results from chronic circulatory insufficiency and consequent inadequate nutrition of the lens due, as Appelmans, Michiels and Missotten[2] pointed out, to the disturbance in ocular metabolism caused by the poor blood supply to the uveal tract. Raeder[45] called attention to the fact that von Michel[35] had advanced the thesis that atheromatosis of the carotid is closely related to opacity of the lens. The so-called senile cataract and the unilateral cataract of unknown etiology can be explained on this basis. Atheromatosis is found, he stated, with striking frequency only on the side of the cataract or is more severe on that side. Bellows and Nelson[7] stated that the transparency of the crystalline lens depends on the proper utilization of nutrient materials supplied by the aqueous and that the most vital requirement of tissue is an adequate supply of oxygen. They said: "The necessary rapid replenishment of oxygen in the aqueous is made possible by rapid diffusion from the ciliary body and by the passage of oxygen from the atmosphere through the cornea. In view of these facts, it is not surprising that lack of oxygen should have adverse effects on the lens, as our experiments have proved." The inefficiency of the circulation to the eye in pulseless disease undoubtedly results in varying degrees of anoxia of the ocular tissues.

Raeder[45] stated that atrophy of the iris is definitely on the basis of nutritional deficiency. The peripheral anterior synechiae simulate those seen in chronic simple glaucoma. Seven of 10 cases of primary atrophy of the iris had glaucoma, he said; but the tension was not elevated in the case he observed, probably because the impaired nutrition interfered with the secretion from the ciliary body. Leo[28] thought that neovascularization at the root of the atrophic iris or in the region of Schlemm's canal probably represents a short-circuiting of the blood supply of the iris or ciliary body. Appelmans, Michiels and Missotten[2] said that the new vessel formation in the iris in pulseless disease differs from the usual type of rubeosis iridis in that it proceeds from the base toward the pupil but leaves the area of the sphincter free. Typical rubeosis affects only the pupillary margin and occurs in association with increased tension. Rubeosis iridis in pulseless disease, they pointed out, is basal rubeosis and is associated usually with hypotony of the globe. According to Redmond Smith[51], neovascularization of the iris is found in thrombotic glaucoma, diabetes, Eales' disease, old retinal detachment, retrolental fibroplasia and cyanosis retinae. He wrote: "It seems reasonable to suggest therefore that a common factor produces the rubeosis iridis in all these diseases and it is suggested that the

common factor is anoxia of the retina. Possibly, as a result of such a retinal abnormality, a metabolite is produced which stimulates new vessel formation. This metabolite may thus give rise to a rete mirabile or the convoluted vessels often seen on the optic disc after central venous occlusion. The metabolite may, however, act vicariously on the iris, producing a new vascular membrane which may occlude the filtration angle and cause thrombotic glaucoma." In reference to the formation of new vessels in the iris, Ashton[4] said: "The concept of a preformed factor diffusing through the vitreous is applicable also to the problem of neovascularization of the iris. It is certainly not without significance that new vessels on the iris so frequently follow the development of retinal disease, wherein the pattern of vascular involvement provides the conditions for production of the vasoformative factor."

It is interesting to consider the factors which are probably responsible for the formation of the peripapillary arteriovenous anastomoses. Caccamise and Whitman[10] and Pinkham[44] stated, without going into details, that the arteriovenous anastomoses are considered to be the result of chronic circulatory insufficiency and impaired nutrition. Shimizu and Sano[49] said that constant severe low blood pressure develops short-circuiting, the arteriovenous anastomoses omitting the finer capillary channels.

Ashton[3] called attention to the similarity between the retinal lesions of pulseless disease and those of retrolental fibroplasia. He has demonstrated that exposure of a newborn kitten to high concentrations of oxygen results in complete obliteration of the ingrowing retinal vessels, but that similar exposure of an adult cat has no effect on the already developed retinal vessels. Ashton[3] commented: "Between these two extremes vaso-obliteration is partial and the more anterior vessels are the most susceptible; in an animal at this intermediate stage of development peripheral vasc-obliteration may be produced by oxygen and the retinal tree is then converted into a series of arteriovenous loops extending for variable distances around the disk, producing a picture exactly analagous to that seen in the late stages of pulseless disease." He added: "Although the etiologic factors are, of course, entirely different in each case, the development of arteriovenous anastomoses in both instances is attributable to gradual obliteration of retinal vessels which first involves the capillary bed and advances in an anteroposterior direction. Furthermore, in both conditions the severe degree of retinal anoxia which results, leads to extensive neovascularization."

According to Ashton[4], there are three basic requirements essential for the stimulation of vessel growth in the immature retina: (1) the presence of living cells to ensure an active metabolism; (2) a low oxygen tension to promote anaerobic metabolism; and (3) a poor venous drainage to permit the accumulation of anaerobic metabolites, wherein the vasoformative factor probably lies. He thought that, probably, the vasoformative factor would be less readily elaborated in the mature retina because its metabolism is largely aerobic. In Ashton's[4] opinion, "intraretinal neovascularization in the mature retina is a rarity, although new-channel formation through obliteration and dilatation of preexisting capillaries is common and has been misinterpreted as neovascularization." However, Michaelson[34], who showed that all retinal capillaries develop embryologically from veins and who proposed that retinal vascular development

occurred in response to an unknown tissue factor present in areas of relative retinal anoxia, stated that the capacity of the retinal veins and capillaries to form new vessels did not disappear at birth, but simply lay dormant.

Wise[56] stated that he had proposed, "that a proper degree of capillary or vein obstruction was the trigger by which this dormant mechanism of Michaelson's was reawakened. Following sufficient obstruction, circulatory stagnation and a state of relative retinal anoxia beyond the obstruction ensued. Under these conditions, the embryologic vasostimulating factor of Michaelson[34] was reactivated. Disordered neovascularization and aneurysm formation thereby resulted from the irregularly dispersed stimulus. Evidence was also presented that so-called retinal microaneurysms were actually aborted neovascular buds developing in response to this same stimulus."

According to Wise[55], the vasostimulating substance, retinal tissue factor x, is not present normally in the fully developed retina and its production in the adult retina results most often from capillary or venous obstruction. Eliasoph[16] stated that arterial obstruction cuts off the supply of oxygen and nutrients and stops the metabolic processes in the retina. But Wise[55] thought that, in pulseless disease, "It is perfectly conceivable that, as the arterial supply to the retina slowly and progressively decreases, a point of retinal oxygenation is reached which is inadequate, but still enough to keep the tissue alive. At this point tissue factor x develops and neovascularization is stimulated. The latter stops with the formation of arteriovenous anastomoses, for in this disease the retinal anoxia is progressive, tissue death ensues, and with tissue death the formation of factor x ceases. . . . Either of the above—slow arterial obstruction or secondary venous obstruction—in pulseless disease would fit into the general concept of neovascularization enunciated in this paper. I would anticipate some transient microaneurysm formation in the viable inner retinal layers of cases of this disease."

TREATMENT OF PULSELESS DISEASE. As noted by Pinkham[44], treatment of the nonsyphilitic cases has been very unsatisfactory. Cataract extraction does not improve vision because of the lesions present in the retina. Removal of a segment of involved artery, periarterial sympathectomy, cervical ganglion sympathectomy and arterial grafts have been suggested. Pinkham's[44] patient had a right cervical ganglion sympathectomy without significant improvement. Mangold and Roth[30] did a bilateral stellate ganglionectomy on their patient and also resected the thrombosed left common carotid artery and made an end to end anastomosis of the superior thyroid artery to the patent internal carotid. The vision was not improved. Mouquin[37] and his co-authors reported improvement in the vision of their patient under treatment with ACTH, but the vision fell again when the treatment was discontinued.

Elliot, Ussher and Stone[17] reported: "Bilateral denervation of the carotid sinus was performed upon a patient suffering from incapacitating syncopal seizures. The probable etiology of this condition was hyperirritability of the carotid sinus mechanism in association with a congenital obstruction to blood flow through the head and arms." The authors stated that the frequency and severity of the attacks were diminished but that cataracts developed after 8 months and a transient left hemiplegia after 10 months.

Summary. Occlusion of the main branches of the aortic arch, the so-called aortic arch syndrome, may be caused by lesions of several different

types. The terms "pulseless disease" and "Takayasu's disease" should be reserved probably for instances of the syndrome occurring in individuals less than 40 years of age in whom the occlusions appear to be the result of arteritis of nonspecific type. Of the 81 cases collected from the literature, which seemed to meet these specifications, 73 (90%) were in women. Although a large number of cases have been reported from Japan and although it was believed for a time that the disease was confined to the Japanese almost exclusively, cases have now been recorded from many varied parts of the world.

The earliest ocular symptoms and signs of the disease, transient episodes of blurring or loss of vision and low pressure in the central artery of the retina, appear to be due to insufficiency of blood supply to the retina which is manifest particularly when the patient is standing, at which time fragmentation of the blood stream in the retinal vessels may be visible ophthalmoscopically. The late ocular manifestations, permanent loss of vision which may be total, atrophy of the retina and iris with neovascularization, the formation of retinal microaneurysms and peripapillary arteriovenous anastomoses and the rapid development of cataracts, result apparently from progressively increasing anoxia of the retina and uveal tract.

Brief recurrent episodes of loss of vision (amaurosis fugax) and relatively low retinal arterial pressure are common to all types of unilateral or bilateral obstruction to the circulation through the internal carotid arteries. But neovascularization in the retina and iris, the formation of arteriovenous anastomoses in the retina and the rapid development of cataract seem to be specific for the type of bilateral occlusion of the common carotid arteries seen in pulseless disease. A satisfactory method of treatment of this disease has not been devised as yet.

ADDENDUM. Since this manuscript was completed, an article has been published in which attention was called to the apparent value of long-term anticoagulant therapy in the treatment of cases of the aortic arch syndrome (**Spittel, J. A., Jr.**, and **Siekert, R. G.**: Proc. Staff Meet., Mayo Clin., **32**, 723, 1957). The authors referred to several recent pertinent articles and reported "dramatic relief" from the intermittent neurologic and visual symptoms which had been complained of by their patient. A mild ischemic retinopathy in the right eye cleared up during the 7-month period of observation; but there was no increase in the retinal diastolic pressure, which was lower in the right than in the left eye.

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SUMMARIO IN INTERLINGUA

(See page 189 for original article)

Alterationes Occurrente In Le Compartimentos De Aqua Del Corpore Durante Le Curso De Acute Insufficientia Renal E Le Relation Inter Illos E Le Excretion De Aqua E Electrolytos

1. Mesurationes in serie del spatios de antipyrina e radiosulfato esseva effectuate in 8 patientes con acute insufficientia renal. In 3 patientes qui se restabliva, acute studios in serie esseva facite relative al effecto exercite per acetazolamido e pitressina super le hemodynamica renal e super le excretion de natrium, kalium, e aqua.

2. Le spatio initial de antiyprina esseva plus que normal in 5 del 8 patientes. In 3 patientes qui superviveva, le spatio initial de antipyrina esseva plus que normal e decresceva significativemente durante le convalescentia e post le restablimento.

3. Le spatio initial de radiosulfato esseva plus que normal in omne le patientes. In 3 patientes qui superviveva, illo decresceva significativemente. In plus, il non occurreva un appreciabile clearance renal additional de radiosulfato ab le plasma durante le phase oliguric del morbo.

4. Un augmento significative del excretion de natrium e kalium esseva demonstrate post le administration de acetazolamido durante le initios del phase diuretic.

5. Le application de iste datos al tractamento de acute disfallimento renal es discutite.

PHYSIOLOGY

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SESSION OF NOVEMBER 19, 1957

SEMINAR ON ION TRANSPORT IN KIDNEY AND HEART

Ion Transport in Isolated Kidney Tissue. R. E. DAVIES, M.A., B.SC., M.SC., PH.D., D.SC. (Department of Biochemistry, School of Medicine, University of Pennsylvania). A few years ago, largely on the basis of work with erythrocytes, it was generally believed that cells are permeable to anions but impermeable to cations and, largely on the basis of measurements on muscle, that sodium is an extracellular cation whereas potassium occurs in high concentration only inside animal cells. The advent of radioactive isotopes and flame photometry has made possible intensive investigations on ion transport in isolated tissues. When freshly-cut slices of guinea pig kidney cortex are incubated for 5 minutes at 37° C. in oxygenated Kreb's physiological saline solution containing α-ketoglutarate, the tissue swells, gains sodium and chloride but loses potassium. On further incubation for 30 minutes these changes are largely reversed. Metabolic energy is used to cause a net accumulation of potassium and α-ketoglutarate, and a net extrusion of sodium, chloride and water. These net movements during recovery from the trauma of slicing are against concentration gradients and are not found in anaerobic conditions, at 0° C. or in the presence of 2:4-dinitrophenol. The energy needed to drive these net movements of ions is a small fraction of that available from aerobic metabolism. The addition of Na^{24}, K^{42}, or Cl^{35} after the recovery period and during the maintenance of a steady-state showed that there is a very rapid turnover of these ions (16%/min. for Na^+, 18%/min. for K^+, 47%/min. for Cl^-). The rates of turnover were still so high at 0° C. anaerobically that the process cannot be, for example, an active extrusion and a passive leakage because the energy required would be much greater than that available from metabolism. Thus though net energy-requiring movements of ions occur, the steady-state turnover is comparable with exchange diffusion or the behavior of ion-exchange resins. (For further data and references see **Whittam, R.,** and **Davies, R. E.,** Biochem. J., **56**, 445, 1954.)

Ion Transfer in the Kidney: The Action of Chlorothiazide. JOHN E. BAER, PH.D., HORACE F. RUSSO, B.S., AND KARL H. BEYER, PH.D., M.D. (Merck Institute for Therapeutic Research, West Point, Pa.) A physiological pattern has emerged for the carbonic anhydrase inhibitors, sulfanilamide and acetazolamide, which involves alkalinization of the urine, depletion of body bicarbonate with metabolic acidosis, and a decline in cation excretion in response to repeated administration. Chlorothiazide, 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide (DIURIL), inhibits carbonic anhydrase *in vitro* but has unique renal characteristics in that (1) it causes a marked enhancement of

chloride excretion, (2) it can enhance sodium excretion at doses which produce a minimal increase in bicarbonate excretion, (3) its effect on potassium excretion is relatively less, (4) it enhances sodium and chloride excretion under conditions of acidosis, and (5) it does not appear to produce metabolic acidosis even upon prolonged administration. These attributes should make chlorothiazide a useful tool in extending our present understanding of ion transfer in the kidney.

Relationship Between Potassium Movement and the Actions of Various Cardiac Drugs. B. KOROL, PH.D. (Pharmacology Department, McGill University, Montreal)* The possible significance of potassium imbalance in the mechanism of action of several cardiac stimulants and depressants has been explored. Using the isolated perfused rabbit heart, coronary flow and heart contractions were recorded concurrently; simultaneous changes in electrograms were also recorded; and, potassium concentrations in the perfusion fluid and in the perfusates were determined and correlated before and after injections of drugs. At least six experiments were performed with each agent, using either normal Locke's solution or potassium-reduced (50% to 75%) or potassium-free Locke as the perfusing fluid.

During perfusion with normal Locke's solution, or Locke's containing 50% of the potassium content, following injections of the cardiac stimulants, epinephrine (100 μg.), norepinephrine (100 μg.) aminophylline (5 mg.), and isoprenaline (1 μg.), there was a marked increased rate and amplitude of contraction, coronary dilatation, and no change in the form of the electrogram. These effects were associated with a marked increased net loss of potassium. During perfusion with 25% potassium Locke or potassium-free Locke, injection of these cardiac stimulants produced potentiated cardiac responses and in addition, marked cardiac arrhythmias. These responses were associated with marked increased net loss of potassium.

During perfusion with Locke's solution, or Locke's containing 50% of the potassium, following injection of acetylcholine (100 μg.), methoxamine (10 mg.), and nitroglycerine (1 mg.), there was marked coronary dilatation with intense depression but relatively slight change (except acetylcholine) in the electrogram pattern. These cardiac effects were always associated with a net gain of potassium. During perfusion with 25% potassium or potassium-free Locke's solutions, injections of these cardiac depressants produced a less marked coronary dilatation and depression, but electrograms now showed definite cardiac arrhythmias associated only with net loss of potassium from the heart.

It is concluded that the potassium shifts resulting from the administration of these agents might act as some type of trigger mechanism and thereby effect heart function.

The Relationship Between Myocardial Potassium Exchange and Heart Rate. HADLEY L. CONN, JR., M.D., AND JOHN C. WOOD, M.D. (Department of Medicine, University of Pennsylvania). Potassium transfer between cells of the myocardium and the surrounding interstitial medium appears to have an important role in producing the electrical currents of the heart and in regulating myocardial contraction. A study of potassium transfer kinetics in the isolated dog heart has been carried out by employing radioactive (K^{42}) tracer techniques. The coronary circulation is perfused with a constant volume of arterial blood. Appropriate

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measurements of the concentrations of K, K^{42}, O_2, CO_2, pH, Cl, Na, and other materials is carried out on the arterial blood, on coronary sinus blood and on the heart muscle. Present experiments have been concerned with the demonstration of those factors, particularly changes in heart rate, which influence potassium exchange. Therefore, experiments were performed on hearts beating from essentially 0 to 180 per minute. Rapid rates were obtained by external stimulation of the atrium and cardiac arrest produced by high serum K concentrations and by acetylcholine. The results show a strong positive linear correlation between potassium exchange and cardiac rate. There is a positive zero intercept suggesting the occurrence of K exchange in the absence of activity, such as is present in resting skeletal muscle. Results show also that external increases in potassium concentration increase exchange during cardiac arrest. The importance of still another parameter, membrane permeability, is apparently emphasized by findings during acetylcholine arrest, at which time exchange is considerably greater than would be anticipated from the established normal regression curve. Finally, there was a much greater exchange in previous experiments on the working heart at comparable heart rates than in these isolated nonworking hearts, suggesting that strength of contraction may affect exchange rates. It is to be concluded that several parameters, perhaps all of those just enumerated, are determinants of potassium exchange in the myocardium.

BOOK REVIEWS AND NOTICES

ORAL MEDICINE: DIAGNOSIS AND TREATMENT. By LESTER W. BURKET, D.D.S., M.D., Sc.D., Professor of Oral Medicine and Dean, School of Dentistry, University of Pennsylvania. 3rd ed. Pp. 558; 351 ills., and 40 color plates. Philadelphia: J. B. Lippincott Co., 1957. Price, $14.00.

DENTISTRY is basically a part of medicine. By reason of its highly specialized nature and particularly its specific technical aspects, it early became completely separated from the parent stem, in some respects to the detriment of both. At the University of Pennsylvania there has long been recognized the need for a closer relationship between these two fields and it is significant that the author of this work is both a physician and a dentist and Dean of the School of Dentistry at Pennsylvania. The appearance of the third edition of this text is good evidence that dentists are becoming increasingly aware of the patient as a whole in diagnosis and treatment. Physicians appreciate the fact that dentists are increasingly recognizing systemic disease through its oral manifestations. The book is well-written and the numerous illustrations are excellent. Physicians as well as dentists should find it a very useful volume.

R. K.

CRYPTORCHISM. By CHARLES W. CHARNY, M.D., AND WILLIAM WOLGIN, M.D., Albert Einstein Medical Center, Southern Division, Philadelphia, Pennsylvania. Pp. 140; 28 ills. New York: Paul B. Hoeber, Inc., 1957. Price, $5.85.

A VAST amount of work by Drs. Charny and Wolgin has resulted in a very excellent treatise on the much discussed subject of cryptorchism. Basing their views and conclusions on information obtained by testicular biopsy, the authors have given urologists, and the medical profession in general, a good working program for the management of the cryptorchid patient. The chapter on pathology is very good and most enlightening because of the very exact and consistent findings in many hundreds of testicular biopsies. The illustrations throughout the book are excellent.

The only possible criticism of this work is perhaps that the authors are a little too dogmatic in their views about treatment. From their pathologic findings, however, these views seem to be warranted.

T. H.

HEREDITY AND YOUR LIFE. By A. M. WINCHESTER, PH.D. Pp. 333; 33 ills. New York: Vantage Press, Inc., 1956. Price, $5.00.

A BIOLOGIST and geneticist with a facile pen has written a book for popular consumption that will be found interesting and informative.

R. K.

ULTRAMICRO METHODS FOR CLINICAL LABORATORIES. By EDWIN M. KNIGHTS, JR., M.D., RODERICK P. MACDONALD, PH.D., AND JAAN PLOOMPUU, Harper Hospital, Detroit. Pp. 128; 18 ills. New York: Grune & Stratton, Inc., 1957. Price, $4.75.

THE authors have gathered together a number of practical ultramicro techniques which should be very helpful to clinical laboratories desiring to perform accurate tests on small volumes of blood. The methods described are designed to include determinations of microgram or microliter amounts. With individual tests requiring 0.01 to 0.03 ml. of serum, a fairly complete survey is possible on 0.2 to 0.3 ml. of blood.

In addition to detailed descriptions of the various tests, there are directions for setting up ultramicro chemistry in the general laboratory, the necessary equipment is indicated, and supply sources noted.

This volume should be particularly useful to laboratories whose hospital has a pediatric service or certain adult patients who offer a special problem such as obesity, extensive burns or other cutaneous involvement.

C. Z.

ANNUAL REVIEW OF BIOCHEMISTRY, VOL. 25, 1956. Edited by J. M. LUCK. Pp. 794; 1 ill. Palo Alto, Calif.: Annual Reviews, Inc., 1956. Price, $7.00.

AFTER a quarter-century, publication of this series of Reviews remains an important annual event. The editors and contributors are to be congratulated on the long-sustained high quality of their writings which so many workers have read with profit. The present volume is also an excellent one. It opens with an interesting biographical sketch of the late Sir Edward Mellanby. Ensuing chapters include summaries of progress in the study of Nonoxidative, Nonproteolytic, and Proteolytic Enzymes, Carbohydrate Chemistry and Carbohydrate Metabolism, Lipide Chemistry and

Lipide Metabolism; the Chemistry of Proteins and Peptides, the Metabolism of Amino Acids and Proteins, and of Purines and Pyrimidines. Other subjects covered include Water Soluble and Fat Soluble Vitamins, Nutrition, Biochemistry of Viruses, the Chemistry of Fungi, and Biological Oxidations. Among other topics reviewed which may be of special interest to clinical investigators are the Hemoglobins, Cholesterol Metabolism, Chemical Constitution and Biochemical Specificity, the Biochemistry of Cancer, and the Metabolism of Drugs and Other Organic Substances. C. Z.

Refresher Course for General Practitioners. Third Collection. Pp. 548; 58 ills. London: British Medical Association, 1956. Price, 25 s.

This is the third volume of collected papers originally written for the benefit of general practitioners and which appeared in the British Medical Journal in 1952 and 1953. Each article has been revised and brought up-to-date by the author for this re-publication. General practitioners will appreciate the reprinting of these timely articles in this convenient collection. R. K.

The Collected Papers of Paul Ehrlich, Vol. 1. Histology, Biochemistry and Pathology. Compiled and edited by F. Himmelweit, M.D., Ph.D., F.R.C.P. (Ed.), Director, Department of Virus Research, The Wright-Fleming Institute, St. Mary's Hospital Medical School, London. With the assistance of Martha Marquardt, and under the editorial direction of Sir Henry Dale, O.M., G.B.E., F.R.S., M.D., F.R.C.P. Pp. 653; 7 ills. London and New York: Pergamon Press, 1956. Price for set of 4 volumes, $85.00.

The centenary of the birth of Paul Ehrlich gave occasion for a reassessment of the impact of this great scientist upon many aspects of medicine. No biography could accomplish this as well as the examination of Ehrlich's writings. The present volume is the first of four which will reprint all of Ehrlich's publications as well as a number of hitherto unpublished writings and addresses. In each instance, the publication is in the language in which it first appeared with the exception of a long article on Anemia, written in German for Nothnagel's System, but here to appear in an English translation. The present volume deals with papers in the field of histology, biochemistry and pathology. Those responsible for this work are to be congratulated for a great service to medical literature and science. R. K.

The Year Book of Pathology and Clinical Pathology, 1956–1957 Year Book Series. Edited by William B. Wartman, B.S., M.D. Pp. 510; 158 ills. Chicago: The Year Book Publishers, Inc., 1957. Price, $7.00.

This volume consists of abstracts of articles taken from various journals which were received January through December, 1956. A number of other articles which the reviewer would consider pertinent to this volume have either been overlooked or otherwise omitted. This is a relatively minor criticism, however, as the included material is generally excellent. Of particular value and timeliness is the extensive coverage of radiation effects. Pathologists and clinical pathologists will find much of interest in these brief abstracts. C. Z.

Hospital Patient Survey. By Howard A. Rusk, M.D. Pp. 146. New York: Goldwater Memorial Hospital, 1956.

One out of every five patients in New York City municipal, general and chronic disease hospitals is there, not because he needs hospital services but simply because he has no place to go. This report attempts an evaluation of the characteristics, medical findings and potential disposition of the patients in the New York Municipal Hospital System, with particular attention to the problems of chronic disease and custodial care. The study contributes valuable observations in outlining the problem and will be helpful to all who are involved in the planning of the care of patients who are the charge of the municipality. R. K.

Systemic Arterial Embolism: Pathogenesis and Prophylaxis. By John Martin Askey, M.D., Associate Clinical Professor of Medicine, University of Southern California. Pp. 157; 22 ills. New York: Grune & Stratton, Inc., 1957. Price, $5.75.

This is a very interesting monograph dealing with the history, etiology and the results of arterial embolism as well as the treatment and prophylaxis. The book goes into considerable detail and summarizes the literature

quite satisfactorily. There are some 281 references. The book is well recommended.

R. T.

ORGANIZED HOME MEDICAL CARE IN NEW YORK CITY. Hospital Council of Greater New York. Pp. 538. Cambridge: Harvard University Press, 1956. Price, $8.00.

THE increasing incidence of chronic disease among older patients has necessitated an ever greater management of patients in their homes rather than in the hospital. Hospitals are, therefore, faced with the problem of extending medical service into the home. This volume analyzes and evaluates the organized plans existing in New York City for extending such medical care to the long-term patient in his home. The material here presented is the most voluminous yet to be published, covering nineteen home medical care programs of which sixteen are operated by municipal hospitals and one each by Montefiore Hospital, The New York Hospital-Cornell Medical Center, and the Department of Welfare. The five sections of the book include: 1) Summary and Recommendations; 2) History and Background; 3) The Patients and Their Families; 4) Analysis of the Home Care Programs in New York City; and 5) The Place of Home Care in Total Medical Care. This is a valuable contribution to the subject.

R. K.

CURRENT THERAPY, 1957. Edited by HOWARD F. CONN, M.D. Pp. 731. Philadelphia: W. B. Saunders Co., 1957. Price, $11.00.

THIS is the newest edition of a work which presents the latest approved methods of treatment for the practicing physician. It has been prepared by three hundred contributors and it contains thirty-nine pages more than the previous edition. All the articles are original and written specifically for this volume. In many instances several contributors have been invited to give their preferred method in conditions in which there is a difference of opinion. This gives the reader an opportunity to exercise his own judgment. The reviewer notes a commendable increase of conservatism in the use of steroid therapy. The book should find a wide appeal.

R. K.

DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE. 2 volumes. Edited by WILLIAM D. STROUD, M.D., Professor of Cardiology, University of Pennsylvania Graduate School of Medicine, and MORRIS W. STROUD, III, M.D., Associate Professor of Medicine, Western Reserve University. 5th ed. Pp. 1,702; illustrated. Philadelphia: F. A. Davis Co., 1957. Price, $35.00.

A NEW edition of this outstanding work in the field of Cardiovascular Disease would in itself be a noteworthy event. This, the 5th edition, is particularly so because it now appears in loose-leaf form. It should, therefore, have an even wider appeal, since replacement pages will keep it constantly abreast of the times. All sections have been brought thoroughly up-to-date and the Index has been materially enlarged.

R. K.

PHYSICAL DIAGNOSIS. BY SIMON S. LEOPOLD, M.D., Professor of Clinical Medicine, University of Pennsylvania School of Medicine. 2nd ed. Pp. 537; 379 ills. and 25 plates in color. Philadelphia: W. B. Saunders Co., 1957. Price, $9.00.

THE reviewer welcomes the second edition of this excellent text. It reflects the mature judgment, clinical acumen and long experience as a teacher and physician of its author. Teachers of physical diagnosis and medical students will particularly value the skillful manner in which physical signs have been correlated with physiologic and pathologic changes in disease. The work is highly recommended.

R. K.

CHRONIC ILLNESS IN THE UNITED STATES, VOL. II. CARE OF THE LONG-TERM PATIENT. Commission on Chronic Illness. Pp. 606. Cambridge: For the Commonwealth Fund by Harvard University Press, 1956. Price, $8.50.

NEARLY a decade ago the Commission on Chronic Illness was created by the joint action of the American Hospital Association, American Medical Association, American Public Health Association and the American Public Welfare Association. Its purpose has been to review and evaluate the chronic illness problem and to be of service in providing correlation and direction to the manifold but unintegrated efforts in the prevention and control of chronic disease. This volume is the first of a series of four in which the Commission will report its findings. The series will also include Volume I: Prevention of Chronic Illness; Volume III: Chronic Illness in a Rural Area; and Vol. IV: Chronic Illness in a Large City. The present volume includes chapters

on The Long-Term Patient, The Patient at Home, Rehabilitation at Home and in Institutions, The Patient in an Institution, Personnel and Education, Coordination and Integration, Research for Planning and Administration, Financing, Conclusions and Recommendations. This is a monumental task and its successful performance will, therefore, be of the greatest importance. The present volume is a highly commendable and long first step in that effort. R. K.

ULCERS OF THE LEGS. By P. PIULACHS, Chief Professor Surgeon in the Faculty of Medicine of Barcelona. Pp. 574; 303 ills. Springfield, Ill.: Charles C Thomas, 1956. Price, $15.50.

CHRONIC ulcers of the legs constitute one of the most difficult problems confronting physicians today. A comprehensive monograph such as this one written by Dr. Piulachs is, therefore, to be received with interest by those dealing with leg ulcers. The author, who is Chief Professor Surgeon on the Faculty of Medicine of Barcelona, Spain, has devoted years to the study and management of leg lesions. It is on this experience that this volume is based.

The material is presented in the following sections: General Conceptions of Leg Ulcers, Ulcers of Venous Etiology, Physiopathology of Ulcers Due to Venous Insufficiency, New Pathogenetic Concept of Varicosities, Evolution of the Venous Thrombosis and of Its Sequelae, Arterial Ulcers, and Trophoneurotic Ulcers (Plantar Perforating Ulcers).

Surgeons and other clinicians concerned with peripheral vascular disease and ulcers of the leg will find much of interest in this well-illustrated book. C. Z.

GOEPP'S MEDICAL STATE BOARD QUESTIONS AND ANSWERS. By HARRISON F. FLIPPIN, M.D., Professor of Clinical Microbioloy, The Graduate School of Medicine, University of Pennsylvania, 9th ed. Pp. 569, Philadelphia: W. B. Saunders Co., 1957. Price, $8.00.

THE ninth edition of this time-honored text has been considerably revised to keep pace with the advances in medicine which have occurred since the previous volume which was written some 7 years ago. The question and answer form continues to be used. The book is up-to-date and covers such recent developments as the newer steroids and antimicrobial drugs, aldosteronism, the newer agents in the treatment of malignant diseases, cardiovascular surgery, the tranquilizers, and others. Illustrations would add much to future editions. This is perhaps the best review volume for anyone preparing for board examinations and would in fact be fruitful reading for all physicians. W. L.

ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO D, MEDICINA, VOL. X, 1955; VOL. XI, 1956. Pp. 529 and 268 respectively; illustrated. Lublin: Nakladem Uniwersytetu Marii Curie-Sklodowskiej, 1956 and 1957.

THESE volumes contain a series of twenty-three articles in various medical fields. All are in the Polish language but are supplemented by abstracts in Russian and English or German. Reference lists include many from western medicine. R. K.

OBESITY, ITS CAUSE, CLASSIFICATION, AND CARE. By E. PHILIP GELVIN, M.D., Associate in Medicine, New York Medical College, and THOMAS H. MCGAVACK, M.D., Professor of Clinical Medicine, New York Medical College. Pp. 146; 19 ills. New York: Paul B. Hoeber, Inc., 1957. Price, $3.50.

THE definition of obesity in the opening paragraph of this monograph includes the statement that an increase in weight above the ideal, unless caused by certain listed conditions, is due to the deposition of fat. However, a few pages further, the importance of heavy muscular development is stressed as a cause of "overweight." The usual actuarial values for morbidity and mortality associated with obesity are reproduced without refference to the recent criticism of Keys of these data. The metabolism of fat and carbohydrate is superficially reviewed; in this section a full page is devoted to a table on the "hexose-monophosphate shunt" with no refference to the important role that this pathway may play in lipogenesis. In their classification of obesity, several endocrine factors are included; there is no reference in this list to hyperinsulinism which may represent the only true endocrine disorder causing obesity. The management of obesity in the final chapters consists of reducing diets, anorexigenic agents and procedural methods for following the course of treatment. The program offered is safe and convenient; attention is given to the principles of sound nutri-

tional practice. This book would be recommended only for general collateral study in this field. It fails to provide an adequate discussion of the basic aspects of nutrition and dietetics for use in teaching or clinical practice. C. S.

LYMPHATICS, LYMPH AND LYMPHOID TISSUE. BY JOSEPH MENDEL YOFFEY, D.Sc., M.D. (MANCH.), F.R.C.S. (ENG.), Professor of Anatomy, University of Bristol, AND FREDERICK COLIN COURTICE, M.A., D.PHIL. (OXON.), D.Sc. (SYDNEY), F.R.A.C.S. (HON.), Sydney Hospital, Sydney. 2nd ed. Pp. 510; 99 ills. Cambridge: Harvard University Press, 1956. Price, $10.00.

SOME years ago an outstanding treatise was written on the lymphocyte and lymphoid tissue by the late Dr. C. K. Drinker and J. M. Yoffey. However, a new edition has been needed for some time in view of the remarkable extension of knowledge in this field. For this reason, the comprehensive revision of this work by Yoffey and Courtice is a timely and welcome one.

The material is presented in eight major chapters: 1) General Arrangement and Organization of the Lymphatic System; 2) The Formation of Lymph; 3) Physiological Significance of Regional Lymphatics; 4) Lymph Flow, Lymph Pressure, and Lymph Composition; 5) Biological Significance of Lymphoid Tissue; 6) Cell Content of Lymph; 7) The Lymphocyte; 8) Practical Considerations.

Although this volume will have a special appeal to hematologists, histologists, physiologists and pathologists, it should also be a helpful reference text for physicians and medical students. C. Z.

NEW EDITIONS

Dermatologic Formulary. From the New York Skin and Cancer Unit, Service of Dermatology. Edited by FRANCES PASCHER, M.D., New York University, Bellevue Medical Center. 2nd ed. Pp. 172. New York: Paul B. Hoeber, Inc., 1957. Price, $4.00.

THE 1957 revision of the Dermatologic Formulary, New York Skin and Cancer Unit, continues the high standard set by the first edition. The material is presented in four main sections: (1) Topical remedies. (2) Systemic therapy. (3) Articles for clinic use. (4) Therapeutic aids. This concise presentation contains more than ample prescriptions for preparations to serve those who need a detailed dermatologic formulary. For example, section one lists 129 topical remedies of all types, even including lozenges. The present edition has been brought up-to-date in all respects. The only major criticism that the reviewer would make is that so many proprietary preparations are listed. Generally speaking, hospital formularies, of which this volume is essentially an example, have a tendency to use official rather than proprietary preparations. This is dictated largely by economic reasons. It is conceded, however, that many of the proprietary preparations are more elegant than the official ones. In spite of this, Dermatologic Formulary is a "must" for anyone interested in the therapy of cutaneous diseases. H. B.

Principles of Microbiology. BY CHARLES F. CARTER, B.S., M.D., Director, Carter's Clinical Laboratory, Dallas, Texas, and ALICE LORRAINE SMITH, M.D., Associate Professor of Pathology, Baylor University College of Medicine. 3rd ed. Pp. 665; 188 ills. St. Louis: C. V. Mosby Co., 1957. Price, $5.00.

THIS is an interesting textbook in that it adds to the usual content of such volumes bits of practical information like the federal regulations for immunization during international travel, outlines for student labs, certain recommended procedures for hospital disinfection and examples of useful contributions of microbes to the human and animal economy. The coverage of new knowledge is spotty; for example, the adenoviruses and C-reactive protein are included, but "pathogenic" *E. coli* and bacteriophage typing of staphylococci are not.

That the authors are aiming at a relatively immature audience such as nurses and medical technologists is apparent from the insertion of study questions after each chapter and a glossary of terms. For such students this book will not only be adequate but stimulating as well. E. S.

NEW BOOKS

The Treatment of Burns. BY CURTIS P. ARTZ, M.D., F.A.C.S., Associate Professor of Surgery, University of Mississippi, and ERIC REISS, M.D., Instructor in Medicine, Washington University School of Medicine. Pp. 250; 199 ills. Philadelphia: W. B. Saunders Co., 1957. Price, $7.50.

AN excellent and practical monograph on all aspects of the burn problem, including mass casualty management. There are numerous well-selected and excellent illustrations. R. K.

Collected Papers of the Mayo Clinic and Mayo Foundation, Vol. 48. Edited by RICHARD M. HEWITT, M.D., JOHN R. MINER, Sc.D., JAMES R. ECKMAN, PH.D., M. KATHARINE SMITH, B.A., CARL M. GAMBILL, M.D., M.P.H., FLORENCE L. SCHMIDT, B.S.E., GEORGE G. STILWELL, M.D., AND GUY WHITEHEAD, PH.D. Pp. 778; illustrated.

Philadelphia: W. B. Saunders Co., 1957. Price, $12.50.

THIS book consists of the Collected Papers of the Mayo Clinic which have been published other than in the Proceedings of the Staff Meetings of the Mayo Clinic or the Mayo Clinic number of the Medical Clinics of North America. The volume is well organized dividing the papers into alimentary tract, genito-urinary, ductless glands, odd circulatory organs, and others. The papers primarily seem to be aimed at the general practitioner and they are the usual Mayo Clinic papers, concise, conservative and to the point. R. T.

The Work of WHO 1956. Pp. 233; 61 ills. Geneva: World Health Organization, 1957. Price, $2.00.

THIS annual report of Director-General Candau gives an impressive picture of the progress and achievement of the World Health Organization in its far-flung services. Those interested in preventive medicine and public health will find it a rich store of information. R. K.

Role of Hospitals in Programmes of Community Health Protection. WHO Technical Report Series, No. 122. Pp. 34. Geneva: World Health Organization, 1957. Price, $.30.

Prevention of Rheumatic Fever. Second Report of the Expert Committee on Rheumatic Diseases. WHO Technical Report Series, No. 126. Pp. 27. Geneva: World Health Organization, 1957. Price, $.30.

Tenth Report of Expert Committee on Biological Standardization. WHO Technical Report Series, No. 127 Pp. 35. Geneva: World Health Organization, 1957. Price, $.30.

Medicine in a Changing Society. Edited by IAGO GALDSTON, M.D. Pp. 166. New York: International Universities Press, 1957. Price, $3.00.

THE New York Academy of Medicine performs a laudable service for the lay public in providing a series of lectures on timely subjects by well-qualified speakers. In this volume are five lectures on psychiatric topics: "Adventure and Security in a Changing World" (by Franz Alexander, M.D.); "Changes in Family Life and Mental Health" (by John A. Rose, M.D.); "What the Laboratory Can Teach Us about Nervous Breakdown" (by W. Horsley Gantt, M.D.); "Organic Factors and Personality Functions" (by William Malamud, M.D.); and finally a very delightful lecture on "Salerno and the Atom" by Iago Galdston, M.D., the Editor of the series. Physicians as well as laymen will find here very pleasant reading. R. K.

The Effects of the Sulfonylureas and Related Compounds in Experimental and Clinical Diabetes. BY RACHMIEL LEVINE AND 92 OTHERS. Pp. 292; illustrated. New York: New York Academy of Sciences, 1957. Price, $4.00.

TWELVE papers presented at a conference on "The Effects of the Sulfonylureas and Related Compounds in Experimental and Clinical Diabetes" held by the New York Academy of Sciences in February, 1957.

New Problems in Medical Ethics, Vol. III. Edited by DOM PETER FLOOD, O.S.B. Pp. 299. Westminster, Maryland: The Newman Press, 1957. Price, $4.50.

THIS is the third volume of the *Cahier Laennec* series of papers by French theologians and physicians stating the Catholic position in various medical problems. The present volume deals with six topics: Castration, The Church and the Dissolution of the Marriage Bonds, Psychoanalysis and Moral Conscience, Psychasthenia, Pain, and Euthanasia. R. K.

Soybeans for Health, Longevity, and Economy. BY PHILIP S. CHEN, PH.D., Professor of Chemistry, Atlantic Union College. Pp. 241; 28 ills. South Lancaster, Mass.: The Chemical Elements, 1956. Price, $3.00.

THE glorification of the soybean. This book furnishes information on the nutritive value of the soybean, on its products, its culture and preservation and on recipes utilizing the soybean. R. K.

New and Nonofficial Remedies, 1957. American Medical Association Council on Pharmacy and Chemistry. Pp. 582. Philadelphia: J. B. Lippincott Co., 1957. Price, $3.35.

ALL physicians will welcome the new edition of this standard work that is a "must" on every physician's desk. R. K.

Principles and Technics of Rehabilitation Nursing. BY FLORENCE JONES TERRY, B.A., R.N., GLADYS S. BENZ, R.N., M.A., DOROTHY MERENESS, R.N., M.A., FRANK R. KLEFFNER, PH.D., AND DEBORAH MACLURG JENSEN, R.N., M.A. Pp. 345;

25 ills. St. Louis: C. V. Mosby Co., 1957. Price, $5.50.

THE increasing complexity of the many aspects of rehabilitation has brought with it a corresponding extensive and skilled participation by nurses. This text is well-suited as an introduction for student nurses to this important field. Of particular value are the numerous references which can be used by graduate nurses as a guide for further reading and self-instruction. R. K.

Malaria. Bulletin World Health Organization, No. 3, 4 and 5, 15, 361, 1956. Pp. 501, illustrated. Geneva: World Health Organization, 1956. Price, $6.00.

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Expert Committee on Insecticides. Sixth Report. WHO Technical Report Series No. 110. Pp. 88; 13 ills. Geneva: World Health Organization, 1956. Price, $.60.

Toxic Hazards of Pesticides to Man. WHO Technical Report Series No. 114. Pp. 51. Geneva: World Health Organization, 1956. Price, $.60.

THE rapid expansion in the number and effectiveness of pesticides to control vectors of disease and to safeguard crops has raised important questions with regard to human health. Chief among these are the possibility of an adverse effect of these substances as possible food and water contaminants, the toxic properties of pesticides for those engaged in their manufacture and use, the effects on domestic animals and fish and measures for protection, including the control of pesticide hazards by regulation. These two reports deal with these important problems. R. K.

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